NAVY MEDICAL DEPARTMENT

GUIDE TO

MALARIA PREVENTION AND CONTROL

"MALARIA BLUE BOOK"

Second Edition

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"MALARIA BLUE BOOK"

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NAVY MEDICAL DEPARTMENT
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MALARIA PREVENTION AND CONTROL

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HOW TO USE THIS GUIDE

Strange that a guide should require a guide, and yet in the seven years since the Navy Department Guide to Malaria Prevention and Control was first published, numerous significant changes in malaria prevention and control have occurred, and have influenced this guide to a greater or lesser degree.

- Chloroquine resistance of P. falciparum has become nearly world-wide, making chloroquine an obsolescent drug in some respects.

- Resistance to other drugs, including Fansidar®, quinine, and mefloquine, is cropping up in numerous locations around the world.

- Chloroquine resistance of P. vivax, long feared, has finally occurred in Papua New Guinea and Irian Jaya.

- An increased appreciation of the significance and spectrum of complicated malaria has developed, along with the need to treat it as a medical emergency, in an intensive care setting whenever possible.

- The demonstration that IV quinidine gluconate is an appropriate substitute for IV quinine, thereby making IV medications universally available for complicated malaria.

- The release of mefloquine for prophylaxis and treatment of malaria. In many respects this is the ideal antimalaria drug, but this status is tempered by its expensive cost, especially for mass prophylaxis.

- Fansidar® has proven too toxic for routine prophylaxis, but retains a special, quite narrow, niche for presumptive treatment of selected febrile episodes.

- Doxycycline has emerged from being a second-line drug, to become one of the workhorses for military malaria prophylaxis.

- Universal testing of Naval personnel for G6PD deficiency has called into question the desirability of routinely prescribing primaquine for all personnel.

- o The development and release of permethrin as a repellent for clothing and other fabrics provides additional protection, and additional duties for malaria discipline.

- o With the obsolescence of chloroquine, the usefulness of the Wilson-Edeson test is largely gone. There is no comparable test for other drugs to monitor compliance in taking malaria chemoprophylaxis.

Thus the good old days, when chloroquine, primaquine, and "C-P tabs," were all one needed to know about malaria, are long gone, never to return. The overriding fact of malaria prevention and treatment today, is that these activities are complicated, and require a great deal of individualized management. The second edition, therefore, cannot help but be longer and more detailed.

In order to help the reader find precisely the information he or she needs, extensive use is made of headings and subheadings in the chapters themselves. These are also listed in the Table of Contents, so the reader can skim that to find the sections of interest. In addition, there is a detailed index. Tables, algorithms, and a comprehensive collection of appendices all provide detailed, often step-by-step, information on specific topics. These too are listed in the Table of Contents.

CHAPTER-BY-CHAPTER SUMMARY:

1. "Introduction" - This can be skipped by everyone except those who like to know the historical perspective of the problem at hand. Discusses the extent of the world-wide malaria problem, the WHO's eradication efforts, and the U.S. Navy's historical experience with malaria.

2. "Geographic Distribution of Malaria" - Provides an overview of where malaria is found throughout the world, and the resistance patterns. Although useful as an orientation, medical personnel deploying on an operation are strongly advised to consult a DISRAP (Disease Risk Assessment Profile), available from the nearest NAVENPVNTMEDU (Navy Environmental and Preventive Medicine Unit), or the NAVENPVNTMEDU itself, for the latest and most detailed information.

3. "Life Cycle and Host-Parasite Interactions" - a brief, painless, discussion of the malaria life cycle. This can be omitted, especially when faced with a sick patient. However, the life cycle is a fundamental bit of knowledge that makes a lot of what follows later, much more logical to understand and follow.

4. "Diagnosis, Clinical Presentation, and Clinical Course" - The first six sections are mandatory reading for all Navy Medical Department personnel who may become involved in a malaria case. They are as important for corpsmen as for physicians, since a corpsman often has the awesome responsibility of being the first person to think "malaria," and thereby start the diagnostic and treatment train in motion. The subsequent sections, dealing with the definition and manifestations of complicated malaria, will primarily be of use to physicians, particularly those whose medical unit has some sort of intensive care capability, and who may therefore have to treat a complicated malaria case. However, the initial manifestation of malaria, seen by the corpsman, may also be that of complicated malaria.

5. "Treatment of Malaria" - The first five sections are mandatory reading for all Navy Medical Department personnel who may become involved in a malaria case, corpsmen as well as physicians. In particular, all personnel must be intimately familiar with Section 5, Patient Transfer and Monitoring Guidelines, and be prepared to put them into effect expeditiously. Special emphasis must be paid to the last paragraph of this Section, which deals with the need to begin treatment promptly, even before the patient is transferred. Details of the use of various antimalarials will primarily be of interest to physicians, however all personnel should be aware of the information discussed under Ancillary Treatment Topics. Physicians, in particular, must be well aware of the last Section, Common Errors of Antimalarial Chemotherapy.

6. "Malaria Prevention and Control in the Military" - A very brief introduction.

7. "Chemoprophylaxis" - This chapter will be of particular usefulness to Medical Department personnel deployed with Marines, Construction Battalions, or other personnel deployed in the field in malarious areas, and who are likely to need to prescribe chemoprophylactic drugs there. It discusses the general principles of prophylaxis, provides a Table and Algorithm to help select the appropriate drug, and discusses each chemoprophylactic drug individually. It also outlines the information which must be documented in each individual's health record regarding prophylaxis (drug prescribed, duration, counseling provided). Information on the proper use of the Wilson-Edeson test is also provided.

8. "Personal Protection Measures for Malaria" - This chapter too will primarily be of use to Medical Department personnel deployed with Marines, Construction Battalions, or other personnel in the field. It provides detailed instructions for the use of repellents (DEET, permethrin), and special

protective clothing such as the mesh jacket or mosquito netting.

9. "Malaria Unit Protection Measures" - This chapter will be of use primarily to Preventive Medicine Technicians (PMTs), Environmental Health Officers (EHOs), and entomologists. It discusses in detail considerations for selecting a site for a field camp, techniques of mosquito surveillance, and environmental mosquito control measures. Other corpsmen and physicians may also find the information useful, either as background information or in the absence of any of the above personnel.

10. "Pharmacology of Antimalarial Agents" - Background information primarily of interest and usefulness to physicians. However corpsmen who prescribe chemoprophylactic agents should also be familiar with the sections covering those drugs they prescribe.

11. "Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency" - Mandatory reading for all Medical Department personnel who prescribe primaquine. Discusses in detail the effect of primaquine in the presence of G6PD deficiency, implications of this, and strategies for prescribing primaquine and dealing with adverse outcomes. This chapter will primarily be of interest to physicians, however circumstances may arise when corpsmen may have to prescribe primaquine, or be responsible for individuals in their units who are taking primaquine.

12. "Navy Responsibilities in Malaria Control" - Who all is involved, from Fleet and Force Commanders on down to the hospital corpsman, and what are their roles and responsibilities.

Appendices - These provide specific information, the nature of which will be self-evident from their titles.

And finally, some thoughts on the nature of this book.

- The goal was to produce a "stand-alone" field manual, small enough to fit conveniently into a seabag, but comprehensive enough to provide workable, pragmatic guidance on nearly any situation a physician or corpsman might encounter, alone, in the field.

- Limited, rigid prophylactic and treatment regimens are no longer appropriate for malaria. An attempt has been made to provide sufficient guidance to allow the physician or corpsman to develop an appropriate solution to any situation, in a relatively straight forward fashion. However the old days of "Don't let 'em think, just tell

'em what to do," as guidance for writing a guide such as this, are gone.

- Whether the manual is too big and too detailed, or insufficient, can only be judged as it is used in the field. However, the intent was to err on the side of too much information, rather than not enough.

- Suggestions to write two guides - one for physicians and one for corpsmen - were considered. However there seemed to be no way to determine where to draw the line delineating what was sufficient information for corpsmen. Such an operation carried a certain risk anyway of arousing the ire of corpsmen insulted at where the line was drawn. Besides, who ever heard of a Navy corpsman who would be content with only his or her own version and would forego obtaining a physician version.

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KEY TO CHANGE 1

Change 1 modified the Second Edition as follows:

- Changes to Chapter 7 recommendations on mefloquine chemoprophylaxis and chloroquine (or chloroquine-primaquine) terminal prophylaxis.

- Correction of minor errors noted in previous errata sheet.

- Updating Appendix 2, Malaria Risk by Country, and Appendix 7, SF 600 sample.

- Scanning all graphics (Appendix 2 and Figures 1,4,5,6) and incorporating these digital images into the computer file containing the manual's text. The printed manual may be ordered from Navy Environmental Health Center. The manual is also alvailable in WordPerfect 6.0 format from the Naval Environmental Health Center library.

CHAPTER ONE

INTRODUCTION

STATEMENT OF THE PROBLEM

Malaria poses a hazard to military personnel and their dependents deployed to, living in, or traveling through areas at risk for malaria. Resistance to standard chemoprophylactic and treatment drugs has been demonstrated in malaria parasites in most parts of the world. Similarly, significant insecticide resistance has been demonstrated in the Anopheles mosquito vectors.

Malaria is commonly debilitating to individuals who lack any immunity to it, and may be fatal if improperly treated. About 1.5 million deaths annually are due to this disease, making it one of the most frequent causes of death worldwide. The World Health Organization estimates there are 100 million cases each year, although one authority, in 1986, estimated that there were 489 million cases. Of these, 234 million were estimated to be due to Plasmodium falciparum, resulting in at least 2.3 million deaths.

Unfortunately, many people are unaware of the risks for acquiring this disease and the severity of its complications. However, the risk of acquiring malaria can be minimized by using the personal protection measures and chemoprophylaxis outlined in this manual. Malaria prophylaxis and control are essential to protect the health of Navy and Marine Corps personnel, and their beneficiaries, and to maintain operational effectiveness.

WORLD HEALTH ORGANIZATION MALARIA CONTROL EFFORTS

Malaria, the most prevalent of all human diseases, has caused more deaths than any other infectious disease. It affects primarily the populations of tropical and subtropical regions of the world where environmental conditions favor stable, infected Anopheles mosquito populations. Outbreaks may develop whenever major displacements of people occur, such as during military conflicts, social upheavals, or natural disasters.

According to the World Health Organization (WHO), 2.12 billion people, representing 42% of the world's population, were living in malaria risk areas in 1987. Except in areas endemic for P. falciparum malaria, the impact of the disease is insidious rather than dramatic. It causes chronic suffering,

results in an increased number of deaths from other causes, and decreases life expectancy. For centuries malaria has also had a profound impact through restriction of economic activities and social progress in large areas of the world.

ERADICATION EFFORTS

In the 1950's, the WHO embarked on a program to eradicate malaria. After some initial successes in areas other than tropical Africa, it became apparent that the goal of malaria eradication was unattainable with available methods of control. Among the technical obstacles encountered were the development of resistance to insecticides by the mosquito vector, and by P. falciparum to chloroquine. Other obstacles were economic, political, and educational. Problems of poverty and illiteracy, commonly but not exclusively seen in developing countries, are major obstacles to malaria control. Funds for medications, insecticides, and other measures are often limited. Simpler methods of control, such as avoiding exposure to mosquitoes, are often not practicable. In the late 1960's, the WHO changed its goal of malaria eradication to one of malaria control, with an emphasis on measures that will bring about a decrease in disease transmission.

Although these circumstances required a change in policy from one of eradication to one of malaria control, 43 (30%) of the 143 countries originally considered malarious had achieved and maintained malaria eradication by 1987. In many countries, the morbidity and mortality caused by malaria, and the prevalence of the disease, have been reduced to low levels. Overall, however, the global prevalence of malaria has increased in recent years. Of the 2.12 billion people living in malarious areas in 1987, approximately 445 million lived in areas where no programs for malaria control had ever been implemented. U.S. military personnel will encounter malaria in many areas of deployment around the world.

FUTURE CONTROL METHODS

In the past, malaria control involved the elimination of parasites in man by drugs, prevention of malaria by the use of personal protection measures, direct attack on the Anopheles female with adulticide insecticides, and control of mosquito larvae. While these methods are still the cornerstones of current malaria control programs, new developments may change future control efforts.

The development and testing of new antimalarial drugs, which started in World War II, continues under the coordination of the Walter Reed Army Institute of Research. Since its

inception, more than 250,000 compounds have been screened in primary tests. This effort includes screening available compounds, as well as the synthesis of new ones.

An area of research which potentially could revolutionize control programs is the development of an antimalarial vaccine. The discovery of methods for growing malaria parasites in the laboratory has made it possible to study the organism's antigens and their stimulation of an immune response. Although experimental malaria vaccine trials in humans are being conducted, their efficacy has been frustratingly disappointing. An effective vaccine for field use probably will not be available for a number of years.

MALARIA IN THE NAVAL FORCES AT WAR - HISTORICAL REVIEW

Communicable and vector-borne diseases have resulted in more casualties than combat-induced wounds and injuries. Historically, malaria has seriously compromised U.S. military campaigns fought in tropical environments. It has been an important disease hazard to Naval Construction Battalions, special warfare personnel, shore support activities, and Marine Corps units. Also at risk have been aviation personnel transmitting malaria transmission areas, line forces, and medical rapid deployment forces. Shipboard personnel have been at risk when visiting ports where malaria transmission was documented. These military needs have driven advances in malaria prevention and control, such as new antimalarial drugs and new methods of chemical and environmental control of the vector.

WORLD WAR I

During 1917 and 1918, malaria accounted for 4,746 new hospital admissions, 68,373 lost man-days, and seven deaths in the naval forces. To reduce the risk of infection, ships had screens installed over the ports and hatches prior to entering a malarious area. Crew members used mosquito netting for berths. After sundown, head nets and leggings were used while standing watches topside. Quinine was used for both treatment and prevention of malaria.

Naval land units in the United States and overseas also waged campaigns against malaria. Control measures included mosquito eradication, screening all buildings, and enforcing the use of head nets and gloves while on sentry duty. Efforts to eliminate the mosquito vector included elimination of larval habitats by applying acid sulfate of soda to marshes, filling swamplands with coral fill, and oiling accumulations of fresh water. Training sites, such as rifle ranges, were carefully

selected to avoid mosquito breeding areas. Despite the serious and persistent efforts made by both shore and afloat commands, malaria continued to be a major problem for naval forces during and after World War I.

WORLD WAR II

From 1941-1945, malaria was responsible for 111,675 new hospital admissions, 3,310,800 lost man-days, and 90 deaths in the naval forces. Plasmodium vivax was responsible for 29% of the deaths and 81% of the admissions. P. falciparum caused 56% of the deaths and 9% of the admissions.

In 1943, the Navy Medical Department's major problems were the malaria and filariasis encountered by the naval forces in the Pacific Islands. In that year alone, an average of 5,332 men were on the daily sick list due to malaria, 4,148 of whom were marines. The noneffective ratios for naval forces and the Marine Corps were 253 and 1,325 per 100,000 average strength, respectively. Construction Battalions in the South Pacific were severely affected by malaria.

Malaria contributed greatly to terminating the courageous defense of Bataan in the Philippines. Among those units which saw the most combat, malaria caused more than five times the number of casualties than did wounds and other battle-related injuries.

When the Japanese occupied Indonesia, the Allies' main source of quinine was eliminated. This created a serious military problem, as Allied forces were engaged in some of the most malarious areas of the world. Consequently, research in synthetic antimalarial drugs was given a higher priority. The Germans, who had synthesized antimalarial compounds as early as 1934, were also attempting to find new and better antimalarials. The French had obtained samples of some of these drugs in 1941. Tests confirmed their high activity against malaria parasites. This information was transmitted to the United States where an extensive program of chemotherapeutic research had already begun.

KOREAN WAR

During the Korean War (1950-1953), malaria accounted for 4,397 new admissions, 49,293 sick-days, and no deaths. P. vivax caused 87% of the malaria cases. P. falciparum only caused 1% of the cases.

Most Navy cases of malaria occurred among Marine Corps personnel, and most manifested symptoms after they returned to

the United States. While in Korea, the troops were given weekly suppressive therapy with chloroquine. Upon an individual's departure from Korea or other malaria endemic region, primaquine was prescribed. However, once troops left Korea, there was a marked decrease in compliance with the primaquine regimen, resulting in many delayed primary attacks of vivax malaria after arrival in the United States.

As had been seen in World War II, the malaria experience of the Marine Corps in Korea was worse than that of the Navy and Marine Corps in other parts of the world (Table 1).

TABLE 1

NAVY MALARIA INCIDENCE DURING THE KOREAN WAR
RATE PER 100,000 AVERAGE STRENGTH

	1950	1951	1952	1953
Marine Corps in Korea	80*	320	570	600
Naval Forces Worldwide	12	98	114	228

* Rate is for August-December 1950 only.

VIETNAM CONFLICT

Malaria had a significant impact on naval forces during the twelve years (1962-1973) of the Vietnam Conflict. There were 21,695 new admissions and 46 deaths reported in 10.5 years of record keeping. Malaria was responsible for 187,478 sick days in the seven years for which data are available.

One of the major differences between this conflict and the Korean War was that the majority of cases were due to falciparum malaria (61%) rather than to vivax malaria (18%). Information as to species causing deaths is incomplete. P. falciparum accounted for 72% of deaths, but none were attributed to P. vivax.

As in other wars, the malaria incidence rate for naval forces in Vietnam was much greater than that for naval forces in general. Malaria was practically nonexistent among shipboard sailors and was relatively rare in the United States, but it was quite common in Vietnam. Consequently, during the Vietnam Conflict, the worldwide malaria rate for naval personnel varied with the proportion of personnel in Vietnam and their incidence rates of malaria. As expected, rates were higher for the Marines than for other naval forces.

While the number of naval personnel in Vietnam doubled from 1966 to 1969, the incidence of malaria increased more than fivefold (Table 2). The Navy Medical Statistics for fiscal year 1969 noted that this precipitous rise in malaria incidence occurred despite ever increasing emphasis on pesticides and prophylactic drug programs. The benefits of these programs were largely negated by changes in combat tactics from the defense of fixed bases to mobile air supported sorties into rural areas. This precluded effective attempts at mosquito control. In addition, combat personnel sometimes avoided taking prescribed chloroquine-primaquine prophylaxis because of undesirable side effects, primarily gastrointestinal discomfort and diarrhea. Finally, the presence of drug-resistant parasites in the five northern provinces of South Vietnam, an area in which the Marine Corps operated, undetermined chemoprophylactic efforts.

TABLE 2

NAVY AND MARINE CORPS MALARIA INCIDENCE
DURING VIETNAM CONFLICT
RATE PER 100,000 AVERAGE STRENGTH IN VIETNAM

TIME PERIOD*	RATE
FY 1966	890
FY 1967	1,710
FY 1968	2,000
FY 1969	4,860
FY 1969	7,160
FY 1970	3,620

*FY = fiscal year; (1 July - 30 June); CD = calendar year. CD 1969 figures are for the last half of CD 1969 only, to allow for the transition from reporting on an FY basis to a CD basis.

Appendix 1 provides a numerical summary of the naval forces' experience with malaria during World War I, World War II, the Korean War, and the Vietnam Conflict.

CURRENT MALARIA EXPERIENCE

In recent years the incidence of malaria among active duty personnel has been low - 24 cases in 1987, 60 in 1988, 67 in 1989, and 144 in 1990. The number of people actually exposed to malaria cannot be determined. The proportion by species varies. In 1987, 58% of cases were falciparum and 33% vivax. In 1988, 15% were falciparum and 58% were vivax. In 1989, 59% falciparum and 31% vivax. In 1990, 48% falciparum and 35%

vivax. Given the small number of cases, the overall species proportions were significantly influenced by the proportions associated with local outbreaks. The proportion by Service also varies. A large majority of cases come from the western Pacific, primarily the Marine Corps amphibious training beaches in Subic Bay, Republic of the Philippines. With increased Marine Corps training in Thailand, increased numbers of cases are originating there. Military operations in Grenada and Panama produced negligible numbers of malaria cases, primarily because of the brief duration of exposure.

Navy activities in the Persian Gulf in the late 1980's were not associated with malaria. There have been no cases of malaria among Navy or Marine Corps personnel due to duty during Operation Desert Shield/Storm. This is attributed to an absence of malaria in Saudi Arabia (except the extreme southwestern corner) and in Kuwait. Army personnel suffered about 15 cases of malaria, acquired during operations in southern Iraq. (Marine Corps forces did not enter Iraq.)

CHAPTER TWO

GEOGRAPHIC DISTRIBUTION OF MALARIA

GEOGRAPHIC DISTRIBUTION OF MALARIA - OVERVIEW

The prevalence of malaria in any specific area varies depending upon the season, the climate, malaria eradication efforts and other factors. Urban areas, particularly the port areas, are often free of malaria even in countries where malaria is endemic. Similarly, malaria is often not found above a particular altitude, which varies from country to country. The prevalence and types of resistance to antimalarials can change rapidly. This chapter is designed to provide an overview of the world-wide prevalence of malaria. As such, it is a generalization, and will not be optimally useful when confronting a specific operational commitment. Detailed, up-to-date, information and recommendations for treatment and chemoprophylaxis can be obtained from the Navy Environmental and Preventive Medicine Units (NAVENPVNTMEDUs), which are listed, including addresses and phone numbers, in Appendix 9, "Malaria Consultants."

A particularly useful service of the NAVENPVNTMEDUs is their production and distribution of country specific DISRAPs (Disease Risk Assessment Profiles), VECTRAPs (Vector Risk Assessment Profiles), and DIVRAPs (Disease Vector Risk Assessment Profiles). DISRAPs provide information as to the prevalence of a variety of operationally important diseases, including antibiotic resistance and prevention measures. VECTRAPs and DIVRAPs provide detailed entomological information relevant to vector identification and control. All three products are updated twice a year, and are available in hard copy or on shipboard computer-compatible floppy disks. (Requesting commands are asked to provide an appropriate number of blank disks.)

The advisability of contacting a NAVENPVNTMEDU to obtain the most current information regarding malaria (and other diseases), prior to a deployment or operation, cannot be over emphasized.

GEOGRAPHIC AREAS OF RISK

The geographic distribution of malaria occurs between 45°N and 40°S latitude. Practically all endemic malaria areas of the world are situated within regions having a mean summer temperature of at least 16°C (60.8°F). Appendix 2 shows the principal regions of malaria transmission as well as the

severity of the threat, as of 1991. Appendix 2 also identifies areas of antimalarial resistant P. falciparum malaria, as of 1991. Appendix 8 lists other sources of current information on malaria risk.

AFRICA

With few exceptions, the threat of malaria is widespread in Africa. Plasmodium falciparum is responsible for most of the malaria in sub-Saharan Africa and in southern Africa. Resistance to chloroquine by P. falciparum is widespread throughout most of this range. Resistance to Fansidar® (sulfadoxine and pyrimethamine) has been reported in Angola, Tanzania, Malawi, and Kenya. In some of the countries, there is high level resistance to these drugs, although not yet of the intensity characteristic of Southeast Asia. There are isolated reports of resistance to mefloquine.

Plasmodium vivax is responsible for much of the malaria in northern Africa. Tunisia, much of Libya, Cape Verde, and the southern part of South Africa currently have limited risks of malaria. Well-conducted antimalarial activities in Algeria and Libya are responsible for the decrease in the number of malaria cases there.

P. vivax malaria is rarely found in black Africans due to the genetic absence of the Duffy antigen on their red blood cells (RBCs). This antigen must be present for vivax parasites to penetrate the RBC. In contrast, an unknown proportion of black Americans have reacquired the Duffy antigen, and are susceptible to vivax malaria.

NORTH AMERICA

Although once endemic for malaria, the United States has eradicated malaria. Most malaria diagnosed here is acquired during foreign travel; however, there are rare outbreaks due to local transmission. The most recent ones were in 1987-1990, in the San Diego, California area. Malaria has also been eradicated in Canada, with only scattered reports of imported cases.

Major areas of Mexico have experienced successful eradication activities. However, transmission persists on the west coast despite intensive control efforts, and in the Yucatan Peninsula.

CENTRAL AMERICA

Malaria exists in all countries in Central America, primarily as P. vivax. Panama has confirmed chloroquine-resistant P. falciparum. Resistance to Fansidar® is suspected.

In most Central American countries, there are areas where the previous gains of malaria control have been largely lost, primarily due to insecticide resistance of the vector. Conversely, in other areas that were originally malarious, transmission has been significantly reduced or eliminated.

THE CARIBBEAN

Eradication programs have eliminated indigenous malaria from most of the Caribbean. Malaria is now endemic only in Haiti and the western part of the Dominican Republic, mainly as P. falciparum. Chloroquine resistance has not been reported.

SOUTH AMERICA

Tropical South America

Venezuela and Guyana were among the first countries to eradicate endemic malaria by using residual insecticides to eliminate the vector. However, in Guyana, natural transmission has recurred after cases were imported from other countries. Currently, most of the malaria in Venezuela is P. vivax, with significant increases in the prevalence of P. falciparum. In Guyana, P. falciparum is most prevalent. There is chloroquine-resistant P. falciparum in both countries. Guyana also reports Fansidar®-resistant P. falciparum.

In the other countries of tropical South America (French Guiana, Paraguay, Bolivia, Colombia, and Peru), transmission occurs in areas that had previously experienced good control or even eradication. For Colombia, Bolivia, and Peru, the current level of transmission is significant. The predominant parasite in all of these countries, other than French Guiana, is P. vivax. In Colombia, P. falciparum is also a serious problem. In French Guiana, P. falciparum is the parasite most often transmitted. P. falciparum resistance to chloroquine has been reported in all of these countries except Paraguay.

The last few countries of tropical South America, Brazil, Ecuador, and Suriname, have had successful eradication efforts in major areas, but transmission has increased in some regions despite active control programs. The major species of malaria

in Brazil and Suriname is P. falciparum. While vivax malaria is the most common form seen in Ecuador, falciparum malaria is also a significant problem. All three countries have reported chloroquine resistance, with Brazil and Suriname reporting Fansidar®-resistant P. falciparum as well.

Temperate South America

Chile, Uruguay, and the Falkland Islands are currently free of malaria. However, the northern part of Argentina still has outbreaks of malaria, mainly due to P. vivax.

ASIA

Southwest Asia

In many of the smaller countries in this region, malaria transmission has been interrupted or eliminated. Currently, only imported cases occur in Cyprus, Lebanon, Jordan, Israel, Kuwait, Bahrain, and Qatar.

In Turkey, Iraq, the United Arab Emirates (UAE), and Syria, local transmission still occurs, mainly due to P. vivax. Setbacks to malaria eradication in Turkey and Iraq are partially due to resistance of the mosquito vectors to insecticides. Transmission of malaria also occurs in parts of extreme southwest Saudi Arabia, Oman, and Yemen where the primary parasite is P. falciparum. Isolated reports of chloroquine-resistant P. falciparum have come from Oman, and Yemen.

Middle South Asia

Malaria is endemic in every country of this region except for the Maldives. The most common threat is vivax malaria, although, there are regions where P. falciparum is the predominant species. Chloroquine resistance is widespread throughout the entire region, except in Bhutan.

Control programs in Afghanistan and Iran have experienced setbacks as a result of resistance of the mosquito vectors to the insecticides and internal political problems. Sri Lanka had a vigorous control program for about twenty years, but cutbacks in control efforts resulted in an increase in the incidence of malaria (including epidemics of vivax malaria). Bangladesh and India have important mosquito vectors that are exophilic (i.e. do not readily enter houses) and therefore are poorly controlled by residual insecticides. However, the malaria incidence has been greatly reduced in certain regions of India and Bangladesh.

Southeast Asia

Malaria is endemic throughout this region except in Brunei Darussalam, and Singapore, where only imported cases occur. One reason for the widespread problem in this region is the existence of important exophilic (outdoor) vectors, which are poorly controlled by residual insecticides, usually used indoors. This problem has been seen in Myanmar (Burma), Thailand, and Vietnam. Another control problem is resistance of endophilic (indoor) vectors to the residual insecticides DDT and dieldrin, as seen in Indonesia.

Control programs have helped in Vietnam and Democratic Kampuchea (Cambodia), where the primary endophilic vectors are still sensitive to residual insecticides. However both of these countries have had significant problems with malaria in recent years, primarily in rural areas. Control programs have been partially successful in Indonesia and Malaysia, where the risk of disease remains widespread, but limited to focal areas.

The predominant malaria species in many of these countries is falciparum. This species is even becoming more prevalent in the northern provinces of Vietnam, where vivax malaria had been the most common form of the disease.

Chloroquine resistance is widespread in all of the malarious areas of this region, including the Philippines. In focal areas of the Philippines, resistance to chloroquine may be very high. Despite this, chloroquine resistance was not seen on the Marine Corps amphibious training beaches (Red, Green, White, Blue,and Purple) on Subic Bay until early 1990, when the first presumed cases were reported. These included both Philippine natives living in the beach area, for whom R-II resistance was documented, and several Marines who failed chloroquine treatment of falciparum malaria. There have also been several reports of Marines with vivax malaria, acquired in the training beach areas, who had recrudescences of their malaria despite treatment with chloroquine and standard primaquine treatment (15 mg per day). The latter raises the possibility that some vivax malaria acquired there may be relatively resistant to primaquine.

Myanmar (Burma), Thailand, Democratic Kampuchea (Cambodia), Vietnam, Malaysia, and Indonesia have reported Fansidar®-resistant P. falciparum. Quinine resistance has also been reported from these areas, especially Thailand, Kampuchea, and Vietnam. There is some evidence of mefloquine resistance in the latter two countries. These multiple drug resistant

parasites contribute significantly to the malaria control failures in this section of the world.

East Asia

Japan, Hong Kong, Taiwan, Macao, Korea, and Mongolia are malaria-free. Although the incidence is decreasing, malaria is prevalent in the east-central and southern provinces of China. The most common species is P. vivax, but highly chloroquine-resistant P. falciparum is also present.

EUROPE

Malaria has been eradicated from Europe other than some small foci in the southern USSR. However, increasing numbers of imported malaria cases are being seen.

OCEANIA

Malaria has been eradicated from Australia where only imported cases now occur. Many of the islands of the South Pacific are free from malaria. The incidence of malaria is very high in Papua New Guinea, and the disease is endemic in Vanuatu (New Hebrides). Falciparum malaria is the primary species in both regions. Despite efforts to control the disease, there is also a high incidence of malaria in the Solomon Islands.

All three of the malarious areas in Oceania have reported chloroquine-resistant falciparum cases. Papua New Guinea has reported Fansidar® resistance. Late in 1989, there were several isolated reports of chloroquine-resistant P. vivax acquired in Papua New Guinea. Subsequent work has confirmed that chloroquine-resistant P. vivax is now established in Papua New Guinea and Irian Jaya.

CHAPTER THREE

LIFE CYCLE AND HOST-PARASITE INTERACTIONS

DEFINITION OF MALARIA

Malaria can be either an acute or chronic infectious disease, caused by protozoan parasites of the genus Plasmodium. The infection is normally transmitted by the bite of a plasmodium-infected female mosquito belonging to the genus Anopheles. Four species of Plasmodium infect man: P. falciparum, P. vivax, P. ovale, and P. malariae. P. falciparum and P. vivax are responsible for over 90% of all cases of human malaria. In order to mature, all four species require an anopheline mosquito host for sexual development and a human host for asexual development.

LIFE CYCLE OF THE PARASITE AND MODE OF TRANSMISSION

The multistage life cycle of the malaria parasite is presented in Figure 1 at the end of this chapter. An infective female anopheline mosquito, while obtaining a blood meal, injects sporozoites into the bloodstream of a susceptible human. The sporozoites travel to the victim's liver where they enter liver cells (hepatocytes). The parasites develop within the liver cells, which eventually rupture, releasing numerous merozoites. The merozoites then invade red blood cells (RBCs) where they mature and multiply asexually. The parasitized RBCs eventually rupture, again releasing merozoites which repeat the cycle by invading other RBCs. Rupture of the RBCs is associated with the symptoms of clinical malaria.

Later in the course of the disease, (3-15 days after the onset of symptoms), some of the merozoites within RBCs differentiate into sexual forms called male and female gametocytes. A feeding female anopheline mosquito ingests the gametocytes during a blood meal. When the male and female gametocytes fuse, a zygote forms in the mosquito's stomach. The zygote becomes motile and penetrates to the outer surface of the stomach where it forms an oocyst. A large number of sporozoites form within each oocyst. The oocysts finally burst releasing numerous sporozoites into the body cavity of the mosquito. Some of these sporozoites migrate to the salivary glands where they may be injected into another human host when the mosquito takes a blood meal. The entire developmental cycle in the mosquito takes 8-35 days, depending to some extent on ambient temperatures.

INCUBATION PERIOD BEFORE SYMPTOMS

The time between sporozoite injection and the appearance of clinical symptoms (the incubation period) is typically 12 to 28 days, depending on the Plasmodium species involved. For P. falciparum, the average incubation period is 9-14 days; for P. vivax, 12-17 days; for P. ovale, 16-18 days; and for P. malariae, 18-40 days. However, the incubation period can range from nine days to three years depending on the parasite strain, the patient's immune status, and the patient's malaria chemoprophylaxis history. Partial or incomplete terminal prophylaxis may prolong the incubation period several weeks past the termination of the medication.

Thus, any person who has traveled to a malaria-endemic area must be considered at risk to develop malaria for up to two years, or longer, after leaving the area.

COMMUNICABILITY OF MALARIA

An individual's blood is infective to the mosquito vector as long as viable gametocytes are present. The period of communicability varies with the species and strain of parasite and with response to therapy. In untreated or insufficiently treated cases, infective gametocytes may be found indefinitely in P. malariae malaria; from one to two years in P. vivax malaria; from one to five years in P. ovale malaria; and generally not more than one year in P. falciparum malaria. The infective mosquito remains so for its life, which is generally less than three months. Malaria is not directly communicable from one person to another, but may be transmitted via blood transfusions, IV drug users sharing needles, or organ transplantation.

SUSCEPTIBILITY AND RESISTANCE TO MALARIA

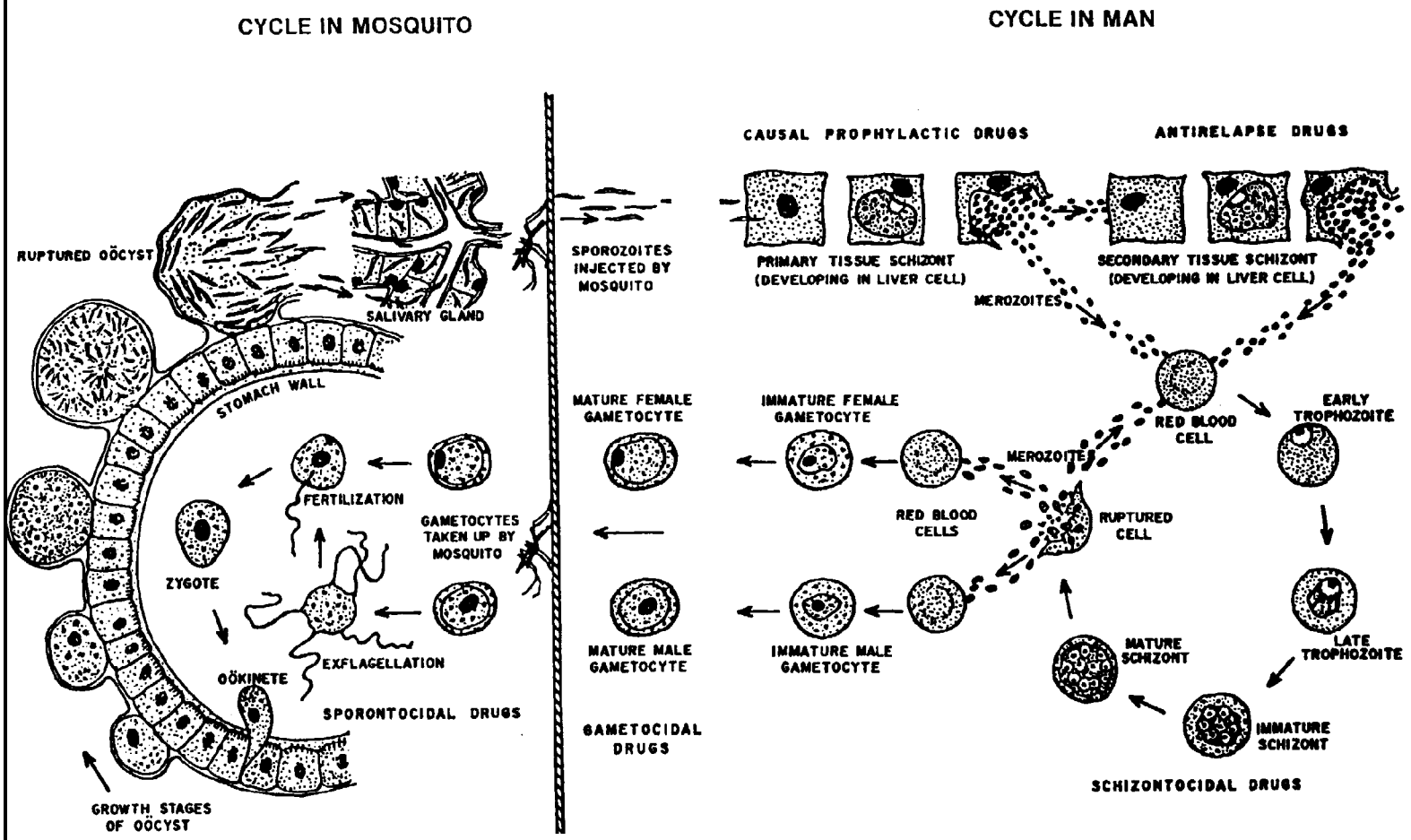
Susceptibility to human malaria is universal except in individuals with certain genetic traits. For example, P. vivax infection is rare in Black Africa, because many Blacks do not have the Duffy antigen, which is necessary for invasion by P. vivax, on their RBCs. Other genetic traits influencing an individual's susceptibility include the sickle cell trait, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Tolerance to infection may be seen in adults residing in highly endemic areas where exposure to infective mosquitoes is continuous. These tolerant adults appear healthy and essentially asymptomatic but have a continuous low level of

infection (parasitemia). They may serve as an unrecognized but important reservoir of infection for susceptible personnel deployed into the area. Once these semi-immune individuals leave malaria endemic-areas, they lose their immunity within about six months.

Chapter Three FIGURE 1

LIFE CYCLE OF PLASMODIUM
THE MALARIA PARASITE



CHAPTER FOUR

DIAGNOSIS, CLINICAL PRESENTATION, AND CLINICAL COURSE

INTRODUCTORY WARNING

No particular sign or symptom is characteristic of malaria.

Chills or rigors, high fever, anemia, and splenomegaly are classically associated with malaria. However, this classic picture is uncommon. The presenting symptoms, severity of attack, and response to treatment may be quite variable depending upon the infecting malaria species, the patient's degree of immunity, whether the patient took chemoprophylaxis, and other factors.

The need for a high index of suspicion, and a willingness to treat presumptively diagnosed malaria, cannot be overemphasized when dealing with patients who are, or were, in a malaria endemic area. Allowing a patient to become seriously ill invites significant complications, makes antimalarial treatment more difficult (primarily because of the need to give potentially toxic drugs intravenously), and worsens the prognosis. The mortality rate for falciparum malaria, if not adequately and promptly treated, can be as high as 25%. Occasionally, other species may also produce fatalities.

PATHOPHYSIOLOGY

RED BLOOD CELL CHANGES AND THEIR EFFECTS

In order to understand better the clinical course of malaria and its potential complications, it is helpful to understand some of the underlying disease processes. These occur when any of the four Plasmodia species infects man, but are particularly important in P. falciparum infections. The three non-falciparum species only infect red blood cells (RBCs) of a certain age, which limits the number of RBCs they can parasitize to less than about three percent of all RBCs. P. falciparum, in contrast, can and does infect RBCs of all ages, theoretically allowing 100% of RBCs to be infected. Infected RBCs subsequently rupture, destroying the RBC in the process and releasing more malaria parasites (merezoites) which then infect additional RBCs. Cases have been reported in which 80% of RBC's were parasitized. The severity, rate of complications, and mortality increase dramatically as the level of parasitemia increases. Levels greater than 10% require that treatment by an exchange transfusion be considered.

Malaria parasites produce most of their effects through changes in the infected RBCs. P. falciparum infected RBCs form "knobs" on their surfaces. The "knobs" cause RBCs to clump together and stick to the lining of the blood vessels. The infected RBCs can also lose their concave shape and become more rigid. As a result of these surface and shape changes, the RBCs sludge in the capillaries, interfering with blood circulation. In addition, parasitized RBCs carry less oxygen and are more fragile than normal RBCs. All of these mechanisms work together to decrease the amount of oxygen carried to vital organs.

DESTRUCTIVE TISSUE PROCESSES

Capillaries become more permeable, allowing fluid to leak into the surrounding tissues. Congested blood vessels and tissue edema causing hypoxia, and hemorrhaging of blood around the blocked vessels, can lead to tissue infarction and necrosis. This process can occur in the brain, spleen, liver, lungs, kidneys, gastrointestinal tract, endocrine organs, and heart. The organs most often affected are the spleen and brain; cardiac changes are usually minimal.

Other factors which contribute to the severity of the disease process are the increased destruction of both infected and noninfected RBCs by the spleen, the destructive rupture of infected RBCs by mature parasites within them, and the decreased production of new RBCs by the bone marrow. These factors result in anemia, which exacerbates the already low oxygen state of the infected individual.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Malaria can and does mimic numerous diseases from influenza to mental illness. It can be especially difficult to distinguish between acute malaria, typhoid fever, and dengue fever. Malaria has been confused with amebiasis, relapsing fever, bleeding ulcers, meningococcemia, acute gastroenteritis, viral encephalitis, typhoid fever and other salmonelloses, tuberculosis, acute endocarditis, influenza, dengue, and scrub typhus among others. The clinical picture may be complicated by having a mixed malaria infection (e.g., P. vivax and P. falciparum) or by a coincidental second illness due to viral (e.g. dengue, influenza) or bacterial (e.g. typhoid, leptospiral) pathogens.

DIAGNOSIS

The diagnosis of malaria must be considered and excluded in all persons seeking medical treatment following travel in an area at risk for malaria. The fact that the individual had taken malaria chemoprophylactic medications does not rule out this diagnosis. Even brief exposures, such as temporarily deplaning at an airport illa malarious area, may be sufficient to allow an infection.

A positive diagnosis depends upon identifying malaria parasites in the peripheral blood. Detailed information on making and interpreting peripheral blood smears in order to confirm the diagnosis of malaria is presented in Appendix 3 of this manual. A low level of parasitemia makes confirming the diagnosis difficult, however a low level of parasites in the blood is not an assurance of mild disease.

FREQUENCY OF OBTAINING MALARIA SMEARS

Although there is no standard recommendation as to how often blood smears should be obtained in order to diagnose malaria, there is a tendency toward too few attempts. Obtaining smears every six to eight hours is usually appropriate. This should be continued until a diagnosis of malaria is made, or until that diagnosis can be confidently ruled out. This may require several days of testing when malaria is a serious consideration. Even after the diagnosis of malaria has been made, peripheral blood smears should still be obtained to monitor the response to treatment. In individuals who are not seriously ill, monitoring once daily is sufficient. Seriously ill patients should be monitored two or three times daily, until there is significant improvement. Monitoring should continue until the parasite level is essentially zero.

QUANTITATIVE BUFFY COAT METHOD

This method, recently developed by a commercial laboratory company, uses a specially prepared capillary tube containing acridine orange, a supra vital stain. Malaria parasites take up this stain, and appear green and yellow when viewed under a fluorescent microscope. The hoped-for advantage of this system is that even laboratory technicians not experienced in diagnosing malaria can quickly and reliably find the bright green and yellow organisms. The method only screens for malaria parasites and the traditional method must be used to identify the specific species causing the infection and to quantify its level of parasitemia. In addition, fluorescent microscopes are not available in the field, and even when available require well trained personnel to operate them. At

this time, this method must be regarded as not appropriate for routine use in the field.

SEROLOGICAL DIAGNOSIS

Malaria can also be diagnosed serologically, but currently available methods have no role in the diagnosis of acute malaria. The antibodies detected by these methods require several weeks to develop, long after the acute infection has occurred. Such tests are useful for epidemiologic surveys.

TREATMENT BEFORE DIAGNOSIS

If an individual is severely ill, it may be necessary to begin treatment before the specific malaria species is identified. If there is doubt as to the particular malaria species infecting the patient, the patient should be treated as if chloroquine-resistant P. falciparum were causing the infection. In some severe cases, when the suspicion of malaria is sufficiently high, it may be necessary to begin treatment before any parasites have been identified. This is not a justification for not attempting to confirm the diagnosis of malaria. It is merely to emphasize that in some cases, initiation of treatment cannot wait for a confirmed diagnosis.

CLINICAL PRESENTATION

SYMPTOMS

Common Presenting Symptoms

Depending upon the stage of infection and the infecting species, a patient may present with a variety of symptoms. Commonly, these may include any combination of mild to moderate malaise, myalgia, backache, headache, dizziness, anorexia, fatigue, nausea, vomiting, diarrhea, and a slight fever. Some patients complain of a dry cough and shortness of breath. The gastrointestinal complaints can be sufficiently prominent as to suggest a diagnosis of gastroenteritis. These symptoms often come and go, leaving the patient feeling well in between times.

This nonspecific prodrome can result in the patient being misdiagnosed, usually as having some sort of viral illness. This delays the initiation of proper treatment. A nonspecific, rather mild illness, is particularly likely in individuals who have taken chemoprophylaxis. The onset of symptoms in falciparum malaria is frequently insidious, but sometimes may be abrupt and dramatic. In rare cases of P. falciparum malaria, the presenting symptoms may be coma, shock, or delirium.

In Navy medical experience, when malaria is misdiagnosed, it is most commonly misdiagnosed as "Viral Illness," "Flu," "Gastroenteritis," or variations of these.

Classic Malaria Symptoms (Not Routinely Seen)

Classically, malaria is described as producing dramatic fever paroxysms. These are associated with the rupture of infected RBCs, and have three stages: cold stage (rigor, chills); hot stage (high fever); and sweating stage (defervescence).

During the cold stage, the patient experiences chills and shaking, appears sallow and may have cyanotic lips and nailbeds. Headache, anorexia, and nausea are usually present, with vomiting and loose stools occurring occasionally. This stage may last a few minutes to a few hours.

The hot stage occurs within several hours. The temperature rises, reaching 104°-106°F (40.0°-41.1°C) (falciparum), or 102°-104°F (38.9°-40.0°C) (other species). The patient feels warm, with warm dry skin. Lightheadedness, fainting, tachypnea, tachycardia, cough, headache, muscle aches, backache, prostration, anorexia, abdominal pain, nausea, vomiting, and/or delirium may occur.

The sweating stage occurs after 3-6 hours. The patient's fever abruptly deferveses (breaks), and he sweats profusely. The patient is weak and tired; his clothes may be drenched.

Classically, the fever paroxysms occur at intervals of 48 or 72 hours. In between, the patient feels well. However, it is dangerously misleading to expect paroxysms or to rely on their presence as a diagnostic clue. It is particularly dangerous to wait for the appearance of fever paroxysms before starting treatment if malaria is suspected. The classic cyclical pattern of paroxysms, if seen, requires several days to emerge. This is because different subpopulations of parasites must develop to the point where they all simultaneously rupture their host RBCs.

In many cases, instead of the classic fever paroxysm, there is a sensation of chilliness, rather than a frank chill, and the "hot" stage may be prolonged and intensified. Marked terminal sweating with an accompanying temperature drop, said to be "characteristic" of P. vivax infections, may not be seen and cannot be relied upon as a useful diagnostic tool.

PHYSICAL FINDINGS

General Appearance

Most physical signs are nonspecific. The patient may seem only slightly ill, or may appear pale and sallow. Sweating may be apparent. Distress or anxiousness may be evident. A depressed level of consciousness, suggestive of cerebral malaria, may be present.

Vital Signs

Tachycardia, up to 120 beats per minute, and tachypnea may be present. The temperature may be normal, especially in the first few days of the i ness, or as high as 105°F (40.6°C). Most patients have a temperature of 102°F (38.9°C) or higher at some time in their illness. The fever may be continuously or irregularly elevated. The blood pressure is often low, e.g. 90-100 mmHg systolic, and often falls further on standing, with associated complaints of lightheadedness and faintness. This orthostatic hypotension, due to fluid loss from sweating, vomiting, diarrhea, and from vasodilation, is common. These processes are exacerbated in hot environments in which relative dehydration and hyponatremia may exist prior to the malarial illness. Orthostatic hypotension responds well to careful fluid resuscitation. Oliguria is common, but usually also responds well to careful fluid resuscitation.

Skin

The skin is often warm and flushed. Cyanosis of the lips and nailbeds may occur with a chill. Urticaria, or a petechial rash, may be seen at a later stage. Jaundice is seen in 10-15% of patients with a high level of parasitemia.

Eyes

Scleral icterus, suffusion of the conjunctivae ("blood shot" eyes), retinal vasospasm and retinal hemorrhage may occur.

Lymph Nodes

Enlarged lymph nodes rarely occur in malaria. If lymphadenopathy is present, a different or additional, disease process is present.

Chest, Lungs, Heart

Examination of the chest may reveal rales, or, rarely, tachypnea, dyspnea, and signs of pulmonary edema or

consolidation. The cardiac exam is usually normal, except for tachycardia. A murmur may be heard secondary to a high cardiac output state, which may be produced by anemia and/or high fever. This high output state can lead to left-sided heart failure.

Abdomen and Gastrointestinal System

The abdomen may show generalized tenderness to palpation. Tender hepatomegaly is uncommon, but a palpable spleen (splenomegaly) is a frequent finding. Sometimes the spleen is also tender to palpation. Rarely, thrombosis and infarction of the spleen may occur. Exercise caution during the physical examination to avoid rupturing the spleen. Massive splenomegaly can be seen even with low levels of parasites, particularly in residents of malaria endemic areas. It may persist for months. Ischemic changes in the blood vessels of the gut, due to RBC sludging, may cause temporary malabsorption, diarrhea or gastrointestinal bleeding.

Splenic Rupture. Malaria is an important cause of spontaneous splenic rupture worldwide, and mortality may be 80% if this rare event is not recognized. Spontaneous splenic rupture is most common in vivax malaria, occurring in 0-0.7% of cases; it is even more rare in falciparum malaria. Acute malaria may present with the same pattern of signs and symptoms as splenic rupture - abdominal pain, fever, tachycardia, prostration, and rapidly developing anemia. Malarial infection by itself can cause severe abdominal pain and guarding, thus mimicking a surgical abdomen. Separating these two diagnostic possibilities requires a high degree of suspicion, and may require the use of standard diagnostic procedures appropriate for an acute abdomen.

Musculoskeletal

Although the patient may complain of myalgia and arthralgia, there are no objective findings to go with these complaints. Peripheral edema is usually absent.

LABORATORY FINDINGS

General

Numerous laboratory tests are commonly abnormal. However, except for the presence of parasites in the peripheral blood smear, the abnormal findings are nonspecific, and generally only mildly abnormal.

Blood

A normocytic, normochromic anemia, leukopenia, and thrombocytopenia are often present during the acute attack. In severe falciparum malaria, the hematocrit may fall to as low as 20 percent, or lower. However the majority of patients with non-falciparum forms of malaria usually show little or no anemia. Despite the hemolysis of RBCs by malaria parasites, these patients are able to compensate by increasing their RBC production. Platelet counts may be as low as 50,000, but hemorrhage rarely results. Laboratory abnormalities indicating disseminated intravascular coagulation (DIC) are common, but clinically important bleeding is rare. Leukocytosis can also be found. Malaria does not cause eosinophilia.

Urinalysis

Trace to moderate protein, urobilinogen, and conjugated bilirubin may be found in the urine. With falciparum malaria, massive hemolysis, hemoglobinuria, and varying degrees of renal failure (blackwater fever) may rarely occur.

Serum Chemistries

An increased BUN and creatinine reflect fever and dehydration, but if the serum creatinine rises disproportionately higher than the BUN, renal failure must be considered. The normal ratio of BUN to creatinine is usually about 10 or 12 to 1.

Hypoglycemia is frequently seen in pregnant patients and in patients with severe malaria. In studies in Thailand and Indonesia, severe hypoglycemia (< 40 mg/dL (2.2 mmol/L)) has occurred in 8% and 15% of patients, respectively. The cause of the hypoglycemia is multifactorial. Parasitized RBCs increase their glucose utilization 75 times over normal. Because falciparum malaria can cause much higher levels of parasitemia, the effect is much greater with this species. Of particular concern, quinine and quinidine, especially when given intravenously, may stimulate insulin secretion resulting in clinically significant hypoglycemia.

The diagnosis of hypoglycemia may be missed because CNS signs and symptoms of hypoglycemia, such as obtundation, may be attributed to cerebral malaria. Hypoglycemia may be seen in the convalescent stage, especially after the patient has received IV quinine or quinidine.

Hypoglycemia should be considered in any malaria patient with a deterioration of his clinical status, especially if the

deterioration involves the CNS. A bolus of 50% dextrose should be administered.

Hyponatremia may also occur. It is associated with excess free water retention, loss of electrolytes due to sweating, vomiting, and diarrhea, and perhaps mild inappropriate ADH secretion. It can be exacerbated by excessive or inappropriate fluid resuscitation.

Serum aminotransferases (SGOT, SGPT) are usually increased. Severe elevation indicates necrosis due to malaria (rare), or an associated hepatitis due to a different cause. Both direct and indirect bilirubin can be elevated. Prothrombin time can be prolonged.

Serum albumin is decreased. Antibody production is significantly and nonspecifically stimulated, resulting in a marked increase in IgM and IgG levels, as well as false positive serologic tests for syphilis (VDRL, RPR).

SUMMARY OF SIGNS, SYMPTOMS, AND LABORATORY FINDINGS

The pattern of signs, symptoms, and laboratory findings can vary significantly from patient to patient. One facility's experience with 50 patients (Minnesota Medicine 1970; 53:331), and a literature review involving 357 patients (Archives of Internal Medicine 1972; 129:607), are summarized in Tables 3 and 4, next page.

TABLE 3

CLINICAL FINDINGS IN MALARIA

	Percent with abnormal findings	
SIGN OR SYMPTOM	**MINNESOTA MEDICINE**	**ARCHIVES INTERNAL MEDICINE**
Fever & Chills	100	Fever 100 Chills 89
Headache	66	89
Nausea & vomiting	64	41
Muscle pain	40	57
Abdominal cramps/diarrhea	16 88	49
Palpable spleen	44	31
Palpable liver		

TABLE 4

LABORATORY FINDINGS IN MALARIA

	Percent with abnormal findings		
FINDING		**MINNESOTA MEDICINE** (Range)	**ARCHIVES INTERNAL MEDICINE**
Anemia	46	5.8 - 12 (Hgb)	25
Leukopenia	36	3,000 - 4,700	25
Thrombocytopenia	80	12,000 -	30
Reticulocytosis	42	150,000	
VDRL positive	16	3 - 18%	30
Bilirubin	46		31
elevated	10	1 - 1.8	
SGOT elevated	17	40 - 108	
Alk p'tase elevated		11 - 27	

These tables may provide some perspective as to the frequency with which different abnormalities may be seen in malaria.

COMPLICATIONS OF MALARIA INFECTION

GENERAL CONCEPTS OF COMPLICATED MALARIA

The term "complicated malaria" includes several critical concepts:

- It is sometimes used synonymously with P. falciparum malaria. However, not all falciparum malaria develops complications, and other malaria species can have complicated courses.

- Most "complicated" cases of malaria, however, are due to P. falciparum. This is because falciparum, unlike the other three species, can parasitize RBCs of all ages, thereby allowing it to develop massive levels of parasitemia.

- The most feared, and perhaps the most important, malaria complication is cerebral malaria. Any decrease in a patient's level of consciousness means cerebral malaria has developed, unless another cause is found.

- All "complicated malaria" must be treated as if it were due to chloroquine-resistant P. falciparum. This means the regimen must include, from the beginning, quinine, or quinidine, or mefloquine. The rationale for this approach is that most complicated malaria is due to falciparum, even if it is not always detected at first, and nearly all areas of the world have, or may have, chloroquine-resistant strains of P. falciparum.

- Almost always, "complicated malaria" needs to be treated with IV antimalarials, at least initially. Cerebral malaria must be treated with IV medications.

- Pregnant malaria patients, whose only "complication" is their pregnancy, may be treated with oral medications if they are not severely ill and can tolerate oral medications. Pregnant malaria patients with complications in addition to pregnancy should almost always be treated with IV antimalarials.

- Mortality from complicated malaria, even with appropriate treatment, may be as high as 15-25%.

- "Complicated" malaria is always a medical emergency.

Critical to a complete understanding of complicated malaria is an appreciation that complications, and mortality, increase

markedly as the level of parasitemia increases. Studies of 2,266 patients in Kuala Lampur in the 1930's and 1940's demonstrated that of those with a level of parasitemia less than 3%, 95% lived. In contrast, of those with parasitemia greater than 3%, 78% died. More recent experience from the U.S. military in Vietnam, and experiences in Bangkok and Irian Jaya, clearly show that renal failure, pulmonary insufficiency, cerebral malaria, and death are all more likely at higher levels of parasitemia. The increase begins at levels of 5-10%, and accelerates rapidly at levels of parasitemia greater than 20%.

DEFINITION OF COMPLICATED MALARIA

A "complicated" case of malaria is a patient with one or more of any of the following features:

- o Hyperparasitemia. This is defined as a level of parasitemia greater than 3%. This level is rarely seen except with P. falciparum infections, however the actual number of parasites in the peripheral blood varies widely within a few hours time.

- o Hypoglycemia. This is arbitrarily defined as a blood glucose less than 60 mg/dL (3.3 mmol/L).

- o Severe Anemia. This is arbitrarily defined as an hematocrit of less than 21%, or a rapidly falling hematocrit.

- o Renal Failure. This is arbitrarily defined as a daily volume of urine less than 400 ml, a blood urea nitrogen (BUN) concentration greater than 40 mg/dL (14.3 mmol/L) , or a serum creatinine greater than 4 mg/dL (307 micromol/L).

- o Hyponatremia. This is defined as a serum sodium less than 125 mg/dL (125 mmol/L).

- o Cerebral Malaria. This is defined as any history or finding of a decreased level of consciousness, or delirium.

- o Prolonged hyperthermia.

- o High output diarrhea and/or vomiting.

- o Any significant impairment of cardiac, renal, or pulmonary function.

- o Pregnancy. Pregnant women are at a higher risk of developing severe and fatal malaria than nonpregnant women. Hypoglycemia affects pregnant women more commonly, and there is an increased risk of spontaneous abortion.

The above parameters are arbitrary ones, and clinical judgment may often determine that action is indicated at an earlier stage of illness, even if that action is nothing more than transferring the patient to a medical facility or unit which can deliver a higher level of monitoring. Equally obvious, the distinction between "complicated" and "uncomplicated" malaria may not be clear cut. The "definitions" listed above are provided more to alert medical personnel that such complications may develop, than to define them.

P. falciparum is notorious for producing, without warning, severe and dangerous types of disease termed "pernicious" or "malignant" malaria. These forms of falciparum malaria carry a mortality rate as high as 50% if not recognized and treated adequately.

MANIFESTATIONS OF COMPLICATED MALARIA

GENERAL MANIFESTATIONS

Profound prostration, shallow breathing, syncope, marked coldness of the skin, subnormal temperature, circulatory collapse, coma, and delirium may be seen.

CARDIOVASCULAR AND PULMONARY MANIFESTATIONS

Anemia and high fever can produce high cardiac output states which can lead to left sided heart failure. Both noncardiogenic pulmonary edema and/or severe intraalveolar hemorrhage may occur. One tenth of falciparum malaria patients have respiratory symptoms such as cough. In a few patients, sudden and severe pulmonary edema develops within several days of therapy. This may be due to, or exacerbated by, fluid overload, but can occur in the presence of a normal pulmonary artery wedge pressure. Chest radiographs show diffuse infiltrates as the patient develops an adult respiratory distress syndrome (ARDS). Among seriously ill malaria patients, bacterial pneumonia is not uncommon, usually due to aspiration. This happens most often when the patient is hyperparasitemic, but may occur when the patient is convalescing.

BACTERIAL SEPSIS AND SEPTIC SHOCK

Bacterial superinfection is not rare in severely ill patients, often presenting as a bacteremia. In addition to bacteremia secondary to aspiration pneumonia, pyelonephritis and/or bacteremia may develop as a complication of urinary catheters. It has been postulated that damage to the gut walls, due to impaired circulation, may allow gut flora direct access to the blood stream. Such bacteremias are usually due to common gram negative organisms, such as E. coli, Klebsiella, and Proteus mirabilis. In otherwise healthy, not previously hospitalized, individuals, these organisms are not usually resistant to common antibiotics, and Pseudomonas is rarely an etiologic agent. IV site infections are another potential source of bacterial infection.

GASTROINTESTINAL MANIFESTATIONS

Severe nausea and profuse continuous vomiting may be seen, along with icterus, jaundice, and epigastric and hepatic tenderness. Extensive vascular involvement of the gastrointestinal tract may cause hematemesis and bloody diarrhea, which exacerbate the anemia. This blood frequently contains immense numbers of parasites. (In the older literature these manifestations were somewhat arbitrarily labeled as "bilious remittent fever" and the "algid form" of pernicious falciparum malaria.)

RENAL COMPLICATIONS

Acute renal failure can be caused by decreased renal blood flow or by intravascular hemolysis. The clinical picture is similar to acute tubular necrosis.

Blackwater fever (malarial hemoglobinuria) is a rare syndrome of acute severe hemolysis, followed by hemoglobinuria, and varying degrees of renal failure. It is seen mostly in persons who have not developed any immunity to malaria, and who have had previous attacks of malaria which were inadequately treated with quinine. It is rarely seen in adults who grew up in, and remain in, malaria indigenous areas. However it may be seen in such individuals when they move from one area to another.

The underlying pathophysiology is unknown, but may be due to a hypersensitivity phenomenon in which autoantibodies are expressed to the partially suppressed falciparum infection. Various triggering factors have been postulated, such as chills or injuries. The hemolysis of black water fever can be sufficiently severe to reduce the hematocrit by 20-50% within

24 hours. It presents as a small amount of dark red or black urine, with a high albumin content and hyaline and granular casts. In severe cases, this is preceded by shock, with a sudden drop in temperature. Accompanying symptoms include hepatomegaly, nausea, vomiting, diarrhea, jaundice, rapid pulse, and in severe cases, a fall in blood pressure. Damage to the kidneys is due not to blockage of the renal tubules, but rather to ischemic changes. The patient may become anuric, with death due to renal failure. In mild cases, the hemolytic crisis passes, and urine volume gradually increases accompanied by clearing of the urine.

CEREBRAL MALARIA - A MEDICAL EMERGENCY

Patients with cerebral malaria are delirious, obtunded, stuporous, or comatose, and the abnormal state of consciousness cannot be attributed to a postictal state, a CNS depressant, hypoglycemia or another infection. All malaria patients with a history or finding of an abnormal level of consciousness, should be considered to have cerebral malaria, until another cause has been proven to be responsible.

This is malaria's most common severe complication, a frequent cause of mortality, and a medical emergency! Prompt administration of antimalarials intravenously is mandatory. The onset may be sudden or gradual, and the clinical presentation may vary.

The patient may complain of progressively increasing headache with little or no fever, then gradually lapse into coma. He may become drowsy and increasingly confused. A clinical picture with little cause for immediate concern may be replaced without warning by a progressive and uncontrollable rise of temperature to levels in excess of 108°F (42.2°C).

Convulsive seizures are common, especially as a presenting symptom in children. They may be directly due to cerebral malaria, or to hypoglycemia or hyperpyrexia. A seizure in a patient with hyperparasitemia is often the first sign of rapid clinical deterioration, commonly into a deep prolonged coma.

Delirium or hallucinations may occur, but localizing signs are quite unusual. In some instances, the onset may be characterized by mania or other acute psychotic manifestation, or the symptoms may suggest acute alcoholic intoxication. The result of such a diagnostic error is usually disastrous.

The physical exam may show contracted and unequal pupils, absent or exaggerated deep tendon reflexes, or a Babinski sign.

There may also be muscular twitching, and jerky or rhythmic movements of the head, neck, and extremities.

The spinal fluid may be either normal or exhibit minor nonspecific changes. Rarely, the spinal fluid pressure may be significantly elevate

CHAPTER FIVE

TREATMENT OF ACUTE MALARIA

Treatment regimens change, sometimes rapidly. Changes may involve medications and dosages, awareness of side effects, or other matters. The regimens provided were current as of July 1991. However all Medical Department personnel who may need to prescribe chemoprophylaxis against, diagnose, or treat malaria should check with their cognizant NAVENPVNTMEDU for any changes in treatment, prophylaxis, or other new information, prior to deployment. NAVENPVNTMEDUs are always able and willing to provide reviews and updated information for malaria (or any other disease of operational relevance) prior to or during deployment.

INTRODUCTION

This chapter deals with the treatment of clinically ill persons infected, or presumed to be infected, with malaria parasites. Chemoprophylaxis, which attempts to prevent individuals from developing symptomatic malaria, is covered in Chapter 7. Before prescribing any antimalarial medication, whether for treatment or prophylaxis, all Medical Department personnel should read Chapter 10, "Pharmacology of Antimalarial Agents," and Chapter 11, "Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency." The present chapter will, for the most part, deal only with the choice of drugs and the doses to be used.

* Figure 2, "Choice of Malaria Treatment Drug," diagrams the key factors in determining an appropriate drug for this purpose. It is located at the end of this chapter.

* Table 5, "Malaria Treatment Regimens," summarizes the drugs and doses used. It is located at the end of this chapter.

The choice of an antimalarial regimen depends upon the infecting malaria species, the possibility that that strain may be resistant to various antimalarials, the ability of the patient to tolerate oral medications, and the presence of malaria complications.

NEED TO BEGIN TREATMENT PROMPTLY

Severe or complicated malaria requires administration of antimalarials as soon as practicable, preferably within an hour of determining that the patient has malaria, even if the species has not been identified. If the patient is severely ill, and there is good reason to believe that he may have

malaria, presumptive treatment for malaria should be started even before examining the peripheral blood smear for parasites. There is less urgency in treating uncomplicated malaria, and it may be treated with oral medications, if tolerated. However treatment should nevertheless begin as soon as practicable after the diagnosis has been made. This is especially true for P. falciparum malaria, which can deteriorate into complicated disease within a matter of hours. Prompt administration of oral medications also may eliminate the need for IV medications at a later time.

COMPLICATED MALARIA - REVIEW

Complicated malaria was defined in Chapter 4. To briefly review, it may include hyperparasitemia (3% parasitemia); a history or findings of an abnormal level of consciousness (cerebral malaria); prolonged hyperthermia; significant pulmonary, cardiac, hepatic, or renal dysfunction; high output diarrhea; or prolonged vomiting. Such patients are considered to be at high risk of even more severe disease or death, and almost always require immediate intravenous therapy, and monitoring in an intensive care setting, if available. Mortality from severe malaria may be as high as 15-25%.

Pregnant patients are not necessarily complicated malaria patients, but are significantly more likely to develop complications. Pregnant patients may be managed with oral medications, if complications are not present when the patient is first seen, but should be closely monitored and switched to IV medications if complications develop. Prompt obstetrical consultation must be obtained if at all possible.

COMPLICATED MALARIA - MANAGEMENT PRINCIPLES

Any patient with complicated malaria requires immediate antimalarial therapy, almost always administered intravenously, and management should be in an Intensive Care Unit. Ideally, monitoring should include frequent monitoring of vital signs, right heart or pulmonary artery wedge pressures, urinary output, hematocrit level, blood glucose, electrolytes, and arterial blood gases. Careful attention must be paid to airway maintenance to prevent aspiration. Fluid and electrolyte therapy must be monitored to maintain adequate cardiac and renal output, without producing fluid overload and pulmonary edema. These, however, are the ideal. It is recognized that operational constraints may preclude applying many of them.

PATIENT TRANSFER AND MONITORING GUIDELINES

Because complications may develop suddenly, and without warning, the following medical evacuation guidelines are offered:

- All cases or suspect cases of malaria should be managed directly by a physician. Units which do not have a physician with them, should transfer the patient to a unit which does have a physician, as soon as practicable. If this is not possible, radio contact should be made with a physician as soon as possible to obtain his or her guidance and advice.

- All cases of complicated malaria, and all cases of falciparum malaria even if uncomplicated, should be transferred as soon as possible to a facility which can provide intensive care monitoring. Ideally this would be a unit with intensive care capabilities. If this is not available, a unit which has a cardiac monitor, or at least an ECG machine, and which can maintain the patient under constant medical observation is acceptable.

- Complicated cases should be admitted directly to an Intensive Care Unit, or whatever facility can best approximate such a unit. Uncomplicated falciparum cases do not have to be admitted directly to an Intensive Care Unit or (facility). However such uncompli-cated cases should be located sufficiently nearby that they can be transferred to the Intensive Care Unit or (facility) within a matter of minutes, if necessary.

- Whenever it is convenient to do so, all cases of malaria, regardless of species or the presence or absence of complications, should be transferred to a U. S. military hospital.

The above are guidelines. They may have to be altered, or perhaps even set aside, to meet whatever operational or other constraints are in effect at the time. However the underlying concept is that malaria may rapidly become complicated and fatal, and Medical Department personnel should not hesitate to transfer a patient to whatever convenient medical facility can offer a higher level of care than their own.

The need to transfer a patient, however, must not delay starting treatment. Antimalarial therapy should be started by the physician or independent duty corpsman who first makes, or seriously considers, the diagnosis of malaria. If IV quinine cannot be given, oral quinine, mefloquine, Fansidar®, or even chloroquine, may provide some benefit until better therapy can

be obtained. If the patient cannot take oral medications, and IV medications are not available, oral medications can be crushed and administered as a slurry through a nasogastric tube.

NEED FOR CHLOROQUINE-RESISTANT, INTRAVENOUS, THERAPY

All patients with complicated malaria should be treated with the same drugs, regardless of the species causing the infection. The medications selected must be effective against chloroquine-resistant P. falciparum, and almost always must be given intravenously. There are several reasons for this approach:

- Although all species may cause complicated malaria, this is most common with P. falciparum. In many cases, a complicated infection felt to be due to a non-falciparum species, is due to a mixed infection, with the falciparum parasites identified at a later time.

- Nearly all parts of the world have, or may have, chloroquine- resistant P. falciparum malaria. Therefore in managing critically ill patients, it must be assumed that they are infected with a resistant strain.

- Regimens effective against chloroquine-resistant P. falciparum will also be effective against the other three species.

- Intravenous therapy is necessary because effective treatment requires rapid reduction of the level of parasites in the bloodstream, through the use of schizonticidal drugs. IV administration eliminates the delay associated with the need to absorb oral medications.

- Intravenous therapy is necessary because patients may be unable to tolerate oral medicines. Even if able to tolerate them, absorption may be inhibited due to impairment of the circulation in the vessels of the gut, and edema of the gut walls.

FREQUENCY OF EXAMINING SMEARS FOR PARASITES

Peripheral blood films should be examined every six to eight hours until the diagnosis of malaria has been confirmed, even though antimalarial therapy may have already been started. Once malaria therapy has been instituted, periodic monitoring of the parasitemia level in the blood smears will help evaluate the effectiveness of the therapy, and help to uncover resistance. If parasitemia is not reduced by 75% at 48 hours

after starting treatment, a high grade (WHO level R-III) of resistance should be suspected.

TREATMENT OF COMPLICATED MALARIA - ALL SPECIES

Two key principles are critical to appropriate management of patients with complicated malaria:

- o Correct, accurate management of fluid status, including careful assessment of hydration status, judicious administration of fluids, and monitoring with a central venous pressure or pulmonary arterial line to prevent the development of pulmonary edema.

- o Rapid reduction of the parasitemia level, generally by IV quinine or IV quinidine.

DRUG OF CHOICE - IV QUININE OR IV QUINIDINE

Although several antimalarials might be used, most are either not rapidly schizonticidal (e.g., tetracyclines, sulfonamides), or not readily available in parenteral form (e.g., Fansidar®). As a practical matter, therefore, all complicated malaria should be treated initially with intravenous quinine or quinidine, followed by some other antimalarial (doxycycline, tetracycline, Fansidar®, or mefloquine) to provide a longer lasting antimalarial effect. Patients who respond promptly to IV quinine or quinidine, may be switched to oral quinine or mefloquine to complete at least three days of treatment with a quinine-type drug, in addition to a second medication.

QUININE/QUINIDINE TOXICITY

In general, the actions and toxicities of quinine and quinidine are very similar, differing quantitatively rather than qualitatively. A statement about one drug usually, or probably, can be applied to the other, with appropriate allowance for the fact that the magnitude of a given effect may differ. Quinidine is somewhat more active than quinine against malaria parasites. It is about four times more likely to demonstrate cardiotoxic effects (primarily prolongation of the QT interval), than quinine. In general, the dose of quinidine used is somewhat less than the dose of quinine.

Minor ECG changes are common, typically a ten percent lengthening of the QT interval, and some T wave flattening. The experience from Thailand with IV quinidine, which is about four times more likely to prolong the QT interval than quinine, demonstrated that the QRS interval had increased by 21% at the end of the fourth dose, from a baseline of 80.5 (+/- 10.9)

msec, to 98.0 (+/- 7.6) msec. The corrected QT interval had increased by 21.4%, from a baseline of 455 (+/- 81) msec to 552 (+/- 132) msec.

An overdose of quinine or quinidine, usually due to too rapid an infusion, may cause convulsions, hypotension, cardiovascular collapse, heart block, ventricular fibrillation, or death. Hypovolemia, due to dehydration or other causes, may predispose IV quinine or quinidine to cause hypotension. Malaria patients should be evaluated, and carefully fluid resuscitated if need be, concurrent with the IV quinine or quinidine. Two separate IV lines should be used, to avoid accidentally infusing the quinine or quinidine too rapidly as part of the fluid resuscitation effort. Fluid resuscitation may be particularly important in patients exhibiting orthostatic hypotension. Quinine is irritating, and can cause necrosis if the IV infiltrates into the tissue surrounding the vein.

WARNING: CONFUSING TERMINOLOGY

In using these two agents, particularly intravenously, it is critically important to pay attention to which drug is being used, quinine or quinidine, and to whether the dose to be used is expressed as the salt (quinine dihydrochloride, quinidine gluconate) or the free base, (quinine base, quinidine base).

ADMINISTRATION AND MONITORING OF IV QUININE/QUINIDINE

Two different IV regimens will be presented. Both regimens require a loading dose, in order to achieve rapidly a sufficiently high steady state level of the drug. Failure to accomplish this, particularly in cerebral malaria, may be fatal to the patient. The basic principle is to dilute the drug in relatively large volumes of fluid, and then to infuse it slowly. Normal saline (NS), 5% dextrose in normal saline (D5NS), and 5% dextrose in water (D5W) have all been used. Because of the volume of fluid required, D5W may provide too much free water for many patients.

Ideally, plasma quinine or quinidine levels should be obtained to monitor for toxicity, and they should be utilized whenever available. However in many operational settings these will not be available. Considerable experience with both these drugs has shown that they can be administered safely without the use of drug levels, by utilizing close electrocardiogram (ECG) monitoring. QRS and QT interval changes are good indicators of quinine and quinidine toxicity, and along with close blood pressure and infusion rate monitoring, provide an effective way to watch for cardiotoxicity. Toxicity which does

develop generally responds to temporary slowing or stopping of the infusion.

The following guidelines, taken from the Centers for Disease Control (CDC) continuous quinidine infusion protocol, are recommended for monitoring for cardiac toxicity anytime IV quinine or quinidine is used:

- The patient should be in an intensive care setting, with continuous cardiac monitoring, if possible. If continuous monitoring is not available, frequent ECG strips or lifepack monitoring should be done.

- Blood pressure should be determined prior to infusion, every five minutes during infusion of the loading dose, and every 15 minutes thereafter.

- An ECG tracing should obtained before beginning the infusion, and every hour thereafter, to determine the QT interval and QRS width.

- The QT interval must be corrected for heart rate according to the following formula:

$$QTc = \frac{QT}{\sqrt{R\text{-}R}}$$

  where QTc is the corrected QT interval, and R-R is the time interval between adjacent R waves.

- The infusion should be temporarily slowed or stopped if the QTc interval becomes longer than 0.6 seconds, the QRS complex widens more than 50% greater than baseline, or hypotension unresponsive to moderate fluid challenge develops. The infusion should be permanently discontinued in the event of persistent severe hypotension (systolic pressure < 80 mmHg), evidence of immediate hypersensitivity reaction to the drug, or a clinically important cardiac arrhythmia.

SPECIFIC QUININE/QUINIDINE REGIMENS

Regimen A: Intravenous Quinine Dihydrochloride

- Administer a loading dose of 20 mg/kg quinine dihydrochloride (16.7 mg/kg base) in 3-6 ml/kg of IV fluid, infused over 4 hours.

- Follow with a dose of 10 mg/kg quinine dihydrochloride (8.4 mg/kg base) diluted as above. This should be

started every 8 hours, and infused over 2-4 hours. The patient should receive a total of three doses, including the loading dose, in a 24 hour period, if needed.

Example: A 70 kg man would receive a loading dose of 1400 mg of quinine, diluted in 210-420 ml of IV solution. Eight hours after the start of the loading dose, he would receive a maintenance dose of 700 mg of quinine diluted in 210-420 ml of IV solution.

- If the patient received quinine or quinidine within the 48 hours prior to starting IV quinine, the loading dose should be omitted. Instead, the patient should be started at the maintenance dose of 10 mg/kg quinine dihydrochloride (8.4 mg/kg base), and continued at this dose every eight hours.

The conversion factor for quinine is: 20 mg quinine dihydrochloride (the salt) = 16.7 mg quinine base.

The parasitemia level frequently rises in the 6-12 hours after initiating IV quinine therapy, but should be less than 25% of the initial level within 48 hours after initiating therapy. If the patient has not responded either clinically or with a reduced level of parasites by 48 hours, the dose of quinine should be reduced by 33%, from 10 mg/kg quinine dihydrochloride (8.4 mg/kg base) to 6.7 mg/kg quinine dihydrochloride (5.6 mg/kg base), to avoid quinine toxicity. It should still be given every 8 hours. Patients with severe parenchymal liver disease should use a dose reduction of 50%, from the beginning.

Usually three or four IV doses will be sufficient to allow changing to oral quinine sulfate, which should be given at a dose of 650 mg p.o. t.i.d. The optimal duration of oral quinine therapy, after IV quinine, has not been determined.

Regimen B: Intravenous Quinidine Gluconate

The following protocol is taken from RE Phillips et al, New England Journal of Medicine, 1985; 312: 1273-1278.

- Administer a loading dose of 24 mg/kg of quinidine gluconate (15 mg/kg base) in 250 ml NS, infused over 4 hours.

- Follow with a dose of 12 mg/kg of quinidine gluconate (7.5 mg/kg base) in 250 ml NS, administered every 8 hours, and infused over 4 hours. The patient should receive a total of three doses in a 24 hour period, including the loading dose, if needed.

- o If the patient received quinine or quinidine within the 48 hours prior to beginning IV quinidine, the loading dose should be omitted. Instead the patient should be started at the maintenance dose, 12 mg/kg quinidine gluconate (7.5 mg/kg quinidine base), and continued at this dose every 8 hours.

The conversion factor for quinidine is: 80 mg quinidine gluconate, (the salt) = 50 mg quinidine base.

When the patient can tolerate oral medications, switch to oral quinine sulfate.

FOLLOW-ON THERAPY AFTER IV QUININE/QUINIDINE

In general, patients should be switched from IV quinine or IV quinidine to oral medications as soon as they can tolerate them. They should receive additional medications to complete seven days of treatment, however several different treatment regimens are available. Patients infected in Southeast Asia require a regimen which considers antimalarial drug resistance patterns found there, and the need for a more prolonged course of a quinine-type drug.

Mefloquine in many respects is the ideal follow-on drug. A single oral dose of 1000-1500 mg is sufficient. This regimen enhances compliance with taking the drug, eliminates the need for other drugs (except primaquine in mixed infections), and adequately (at least for the present) treats resistant P. falciparum strains in Southeast Asia. **WARNING**: The manufacturer's package insert states that if quinine or quinidine is used in the initial treatment of severe malaria, mefloquine administration should be delayed at least 12 hours after the last dose of quinine or quinidine. This is to avoid potential cardiotoxicity from a possible additive effect of administering mefloquine on top of quinine or quinidine. Experience with such a regimen is quite limited, however.

NOTE: The follow-on regimens in the next paragraphs are based on the assumption that essentially all complicated malaria is due to P. falciparum, or, rarely, a mixed infection of falciparum and an additional species. (In the latter case, primaquine may also be required.) In the unusual event that a complicated malaria infection is conclusively demonstrated to be due only to a non-falciparum species, treatment may be continued as if the infection were due to P. falciparum, or switched to a regimen appropriate for the particular non-falciparum species.

Follow-on Therapy - Southeast Asia Infections

Patients who became infected in Thailand, Laos, Democratic Kampuchea (Cambodia), or Vietnam, and perhaps in adjacent countries, should receive a more intensive follow-on regimen. Fansidar® is not recommended, since it will probably have a significant failure rate. Either of the two following regimens may be used.

Regimen A:

Quinine sulfate 650 mg, p.o, t.i.d. to complete 7 days' treatment with a quinine-type drug, including the IV quinine or quinidine

plus Doxycycline 100 mg, p.o., b.i.d., for 7 days

(Tetracycline may be substituted for doxycycline at a dose of 250 mg, q.i.d.)

Regimen B:

Mefloquine 1000-1500 mg, p.o., once

Follow-on Therapy - Infections Acquired Outside Southeast Asia

Any one of the three following regimens may be used.

Regimen A:

Quinine sulfate 650 mg, p.o., t.i.d. to complete 3 days' treatment with a quinine-type drug, including the IV quinine or quinidine

plus Doxycycline 100 mg, p.o., b.i.d., for 7 days

(Tetracycline may be substituted for doxycycline at a dose of 250 mg, q.i.d.)

Regimen B:

Quinine sulfate 650 mg, p.o., t.i.d. to complete 3 days' treatment with a quinine-type drug, including the IV quinine or quinidine

plus Fansidar® three tablets, p.o., once

Regimen C:

Mefloquine 1000-1500 mg, p.o., once

TREATMENT OF UNCOMPLICATED MALARIA

GENERAL PRINCIPLES

Uncomplicated malaria is generally treated with oral medications, which should be started promptly before the patient becomes sufficiently sick that IV medications are required. This is especially important with P. falciparum malaria, which can very rapidly develop complications. Patients who are vomiting, or sufficiently nauseous that they cannot take oral medications, by definition have complicated malaria and should be treated as such. Occasionally a patient may be unable to take oral medications for reasons not related to his underlying malaria. In this case, IV medications must be given, using one of the regimens for complicated malaria.

The combination chloroquine-primaquine (C-P) tablet is intended only for chemoprophylaxis, not for the treatment of acute clinical malaria. If C-P tablets are used for treatment, the result is to administer an inadequate dose of chloroquine, or a greatly excessive dose of primaquine.

When Fansidar® or either of the tetracyclines are used in association with oral quinine, they may be started at any time when the patient is taking quinine. However, their administration must at least partially overlap the administration of the quinine.

P. falciparum - SOUTHEAST ASIA

For purposes of this treatment regimen, Southeast Asia includes Thailand, Laos, Democratic Kampuchea (Cambodia), and Vietnam. It may include adjacent countries, especially in the future if multidrug resistance spreads. Consultation with a NAVENPVNTMEDU is advised. Fansidar® is no longer considered reliable in this area. Either of the following regimens may be used.

Regimen A:

Quinine sulfate 650 mg, p.o., b.i.d., for 7 days

plus Doxycycline 100 mg, p.o., b.i.d., for 7 days

(Tetracycline may be substituted for doxycycline at a dose of 250 mg, q.i.d.)

Regimen B:

Mefloquine 1000-1500 mg, p.o., once

P. falciparum - OTHER THAN SOUTHEAST ASIA

The following regimens are to be used for infections acquired anywhere else in world, except selected parts of Central America and the Caribbean, (See below). They were selected on the assumption that falciparum malaria in these areas is, or may be, resistant to chloroquine. Any one of these three regimens may be used.

Regimen A:

Quinine sulfate 650 mg, p.o., t.i.d., for 3 days
plus Doxycycline 100 mg, p.o., b.i.d., for 7 days

(Tetracycline may be substituted for doxycycline at a dose of 250 mg, q.i.d)

Regimen B:

Quinine sulfate 650 mg, p.o., t.i.d., for 3 days

plus Fansidar® 3 tablets, p.o., as a single dose

Regimen C:

Mefloquine 1000-1500 mg, p.o., once

P. falciparum - ISOLATED CHLOROQUINE-SENSITIVE AREAS

In a few countries, P. falciparum currently remains sensitive to chloroquine. These include Central America north and west of the Panama Canal, Haiti, the Dominican Republic, and in the Middle East, Turkey, Syria Egypt, Iraq, the United Arab Emirates (UAE), and Saudi Arabia. Uncomplicated P. falciparum infections acquired in these countries can be treated the same as uncomplicated P. vivax infections, except that primaquine is not needed. Alternatively, the same three regimens listed in the previous section, "P. falciparum - OTHER THAN SOUTHEAST ASIA," may be used. Because chloroquine resistance continues to spread, a NAVENPVNTMEDU should be consulted prior to deployment for the latest information on chloroquine resistance in these areas.

P. vivax OR P. ovale - WORLD-WIDE

Chloroquine is the drug of choice for initial treatment. Doxycycline, tetracycline, and quinine are also effective, although the tetracyclines may be somewhat less active than chloroquine. Fansidar® is somewhat less active than chloroquine.

NOTE: Chloroquine-resistant P. vivax has been reported from Papua New Guinea and Irian Jaya. A definitive treatment regimen for P. vivax infections acquired in these areas has not been identified, however a regimen for chloroquine-resistant P. falciparum infections should be appropriate. Primaquine for radical cure is also required. Consultation with a NAVENPVNTMEDU is advised.

These two species produce hypnozoites, an exoerythrocytic stage, which remain in the hepatocytes (liver cells). Most drugs, including chloroquine, quinine, quinidine, mefloquine, the tetracyclines, and Fansidar®, do not eradicate hypnozoites. This failure allows malaria relapses to occur at a later date, when additional parasites leave the liver cells. Primaquine is required for complete eradication of the hypnozoites, and prevention of relapses (radical cure). Factors to be considered in prescribing primaquine are discussed in subsequent paragraphs.

Initial Treatment

Chloroquine phosphate 500 mg tablet (equivalent to 300 mg base)

2 tablets p.o. initially (day 1)
followed by 1 tablet p.o. 6 hours later (day 1)
followed by 1 tablet p.o. on day 2
followed by 1 tablet p.o. on day 3

(The total dose is 2500 mg of chloroquine phosphate or 1500 mg of chloroquine base.)

Radical Cure

Primaquine phosphate 26.3 mg tablet (equivalent to 15 mg base)

Regimen A:

1 tablet p.o., daily, for 14 days

(Total dose is 14 tablets)

Regimen B:

3 tablets p.o., as a single dose, once a week for each of 8 weeks

(Total dose is 24 tablets)

Before prescribing primaquine, all Medical Department personnel must read the "Primaquine" section of Chapter 10, "Pharmacology of Antimalarial Agents," and Chapter 11, "Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency."

G6PD normal individuals with confirmed P. vivax or P. ovale infection should undergo radical curative treatment with primaquine. Either of the above regimens may be used. The 14 day regimen may be more convenient for patients, and therefore it may promote compliance.

G6PD deficient individuals with similar confirmed infections should also undergo radical curative treatment with primaquine. However only the eight week regimen should be used. Ideally, quantitative G6PD deficiency testing would be done prior to beginning treatment with primaquine. Such treatment should be undertaken only in consultation with a fully trained infectious disease or tropical medicine specialist, or general internist, with full awareness of the potential risks of administering primaquine to G6PD deficient individuals.

The primaquine regimen must overlap at least one dose of chloroquine. That is, the primaquine must be started no later than one week after the last dose of chloroquine. If the primaquine is delayed until after the patient has completed taking chloroquine, one additional tablet of 500 mg chloroquine phosphate (300 mg base) should be given at the same time (same day) the primaquine is started.

P. malariae - WORLD-WIDE

Treatment is the same as for P. vivax, however terminal treatment with primaquine is not required.

MIXED SPECIES INFECTIONS - WORLD-WIDE

In general, a treatment regimen should be chosen which will be active against the P. falciparum component of the infection. Such a regimen will also be effective against other species, however primaquine may need to be added if P. vivax or P. ovale species are involved.

ANCILLARY TREATMENT TOPICS

GENERAL CONSIDERATIONS

Uncomplicated malaria, in many parts of the world, is managed on an outpatient basis. This usually includes falciparum malaria, if the patient is felt to be reliable. In part, however, this is due to necessity. The standard of care

in Navy medicine is to admit all malaria patients to a hospital, or if that is not available, to a facility where they can be under the direct care of a physician. If this is not available direct communication and consultation with a physician must be obtained. Non-falciparum malaria, and uncomplicated falciparum malaria, can be managed on a hospital ward. The important services needed are: the ability to observe the patient closely for the development of complications, and to monitor routine vital signs, including temperature, pulse, blood pressure, respiratory rate, weight, intake and output, and levels of parasitemia.

Patients with complicated malaria may develop a variety of additional complications, including pneumonia (primarily aspiration pneumonia); pulmonary edema including adult respiratory distress syndrome (ARDS); acute renal failure; gram negative sepsis and septic shock; metabolic acidosis; and cardiovascular collapse. These are all managed the same as in any non-malaria patient, including the use of oxygen, mechanical ventilation, diuretics, fluid resuscitation, vasopressors, and dialysis, as needed. However in addition, it is vitally necessary to reduce the underlying parasitemia as rapidly as possible. In all complicated malaria patients, good nursing care, with admission and daily weights, frequent close monitoring of vital signs including intake and output (using a bladder catheter if necessary), and other clinical and laboratory parameters, is critical.

Much of what follows is directed primarily towards the patient with complicated or severe malaria.

WARD CARE

Severely ill patients are often lethargic, obtunded or comatose, and subject to all the usual complications of patients in that condition. The airway should be kept clear, and the usual precautions taken to prevent aspiration, especially if the patient is vomiting.

Patients with complicated disease should rest on their sides to minimize aspiration, and be turned every two hours to prevent bedsores. Patients should be kept in a screened or air conditioned area, if available, until they are no longer infectious. This precaution prevents such patients from serving as a malaria reservoir from which mosquitoes can feed and then spread the disease to other personnel.

ANTIPYRETICS AND FEVER CONTROL

Patients should be given antipyretics to help make them feel more comfortable, and to minimize development of febrile seizures, which are associated with temperatures over 101.3°F (38.5°C). Temperatures between 103.1°-107.6°F (39.5°-42°C) are associated with delirium, and temperatures over that, with coma. A prolonged febrile period (temperature > 104°F (40°C)) is associated with a poor outcome. Patients with prolonged severe hyperthermia not responsive to antipyretics should be cooled with fanning and sponging, or a cooling blanket if available. Sponging should be done with tepid water, i.e. cooler than body temperature but not cold. If the water is too cold, vasoconstriction will occur in the skin, resulting in heat being trapped in the body core. Alcohol should not be used to sponge patients. The resulting vapors are toxic to patient and staff.

FLUIDS AND ELECTROLYTES

Dehydrated hypovolemic patients may become hypotensive, oliguric, and progress to acute renal tubular necrosis. Over rehydration may precipitate irreversible pulmonary edema.

Common errors in fluid and electrolyte management include the failure to examine the patient thoroughly (e.g. skin and ocular turgor, postural change in blood pressure, urine volume and specific gravity), failure to maintain fluid balance charts, failure to weigh the patient daily, use of excessive and unnecessary hypertonic solutions, too rapid transfusion without first administering a diuretic to help prevent fluid accumulation, failure to assess urine output (undisciplined urination or failure to pass a urethral catheter), failure to include blood, bicarbonate, and the fluid vehicle for antimalarial drugs in the fluid balance calculations, and failure to ask the patient, friends or relatives about fluid intake and output during the 48 hours prior to admission.

IV fluids are necessary only for those patients with orthostatic hypotension, or with complicated disease. Sufficient fluids should be given to maintain an adequate blood pressure and renal perfusion, however care must be taken to prevent pulmonary edema from fluid overload. Mild hyponatremia is common, but clinically unimportant. A serum sodium below 120 meq/L (120 mmol/L) requires emergency treatment.

Fluid therapy and monitoring are accomplished with IV fluids, bladder catheterization, frequent careful clinical exams and monitoring of input and output. If an Intensive Care Unit is available, right heart or pulmonary artery

catheterization and frequent monitoring of electrolytes, BUN, creatinine, glucose, and arterial blood gases are desirable.

HYPOGLYCEMIA

Hypoglycemia may be seen in malaria for two reasons. Parasitized RBCs utilize glucose at a rate 75 times greater than normal RBCs. Of particular concern, however, is the fact that quinine and quinidine, especially if given IV, may stimulate insulin secretion resulting in clinically significant hypoglycemia. This complication may be missed because signs and symptoms of hypoglycemia may be attributed to malaria, e.g., obtundation may be attributed to cerebral malaria.

Even though quinine and quinidine may promote hypoglycemia, neither this possibility nor the actual appearance of hypoglycemia is a reason not to use, or to stop using, these drugs, if they are clinically indicated. The need to treat the parasitemia overrides the risk of hypoglycemia. If hypoglycemia occurs, it should be managed appropriately and the quinine or quinidine continued.

Blood glucose levels should be monitored every six hours in complicated malaria, and any time there is clinical deterioration. This can be accomplished at the bedside with fingerstick techniques such as the Ames Dextrostix. Hypoglycemia less than 60 mg/dL (3.3 mmol/L) should be treated with 50% dextrose (1-2 mg/kg, IV push), followed by a four hour infusion of 10% dextrose, typically at a rate of 100 ml per hour in adults. If the blood glucose level is greater than 60 mg/dL (3.3 mmol/L) at the end of the infusion, the infusion can be changed to 5% dextrose, with continued monitoring of the blood glucose every six hours. Administration of additional dextrose after the initial bolus can be varied to meet individual patient needs. However appropriate monitoring of blood glucose levels is critical, until the levels have stabilized at an acceptable level. If blood glucose levels cannot be obtained, a trial of 50% dextrose should be given to all malaria patients with any deterioration of clinical status, especially if they involve deteriorating mental status.

(Use of product names is for identification purposes only, and does not imply endorsement.)

ANEMIA

In most cases, no treatment is required. If the hematocrit is falling rapidly, or is less than 20 percent, the patient should be transfused with packed RBCs or whole blood. If whole blood is used, the patient should be monitored carefully to

avoid pulmonary edema due to fluid overload. It may be necessary to give diuretics to prevent this.

CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT

All patients with evidence of CNS involvement should have a lumbar puncture to rule out a coincidental meningitis or encephalitis. In cerebral malaria, any combination of symptoms and signs indicative of severe and extensive involvement of the brain may be seen. There are no constant or significant changes in the spinal fluid. The spinal fluid pressure however, may be significantly elevated.

The fundamental treatment for cerebral malaria is to reduce the parasitemia as rapidly as possible. No other treatment is necessary, or effective, except good supportive and nursing care, and in some patients, anticonvulsants. Corticosteroids should not be used. They are of no benefit, and may be associated with complications such as prolongation of coma, pneumonia, and gastrointestinal bleeding.

Seizures should be managed with standard anticonvulsant regimens, although treatment of status epilepticus may be required in some cases. Remediable causes of seizures, such as hypoglycemia or hyperpyrexia, should be identified and corrected.

EXCHANGE TRANSFUSION FOR HYPERPARASITEMIA

If the patient's level of parasitemia is 20% or greater, the chances of complete recovery, even with appropriate antimalarial chemotherapy and supportive measures, are less than 50%. For this reason, exchange transfusion has been recommended for patients with high levels of parasites. Suggested criteria for transfusion are a level of parasitemia greater than 10-15%, or a parasitemia greater than 5% in the presence of cerebral malaria. Transfusion should be continued until the parasitemia decreases to 1-5%.

The rationale for exchange transfusion is theoretical: It removes parasitized RBCs and RBC debris which promote RBC sludging. It may also remove unknown metabolic waste factors and toxins.

Exchange transfusion is usually done manually. One unit of blood, (approximately 500 ml), is removed from the patient over one to two hours. It is then replaced by blood products equivalent to a single unit of whole blood.

The first dose of IV quinine or quinidine should be given before the exchange transfusion. If the patient is severely anemic, this should be corrected before the exchange transfusion begins.

Limited data (five patients) indicate that most of the parasite burden is removed early in the process, with the burden falling by about half within the first four or five exchanges. The quinine or quinidine level falls slightly with each exchange, but quickly returns to baseline. The number of exchanges to carry out in any given patient has not been determined, and there is probably no absolute number. In different studies, from four to 27 exchanges have been required; often, eight to ten units is sufficient to reduce the parasitemia to 1% or less in adults.

Rather than carrying out a predetermined number of exchanges, it is preferable to continue the process until the parasitemia has been reduced to a desirable level.

Exchange transfusions deplete clotting factors, therefore replacement with appropriate clotting factors (e.g. fresh frozen plasma) and platelets may be necessary. As an alternative, whole blood may used, to provide the necessary clotting action. However care must be taken not to fluid overload the patient.

BACTERIAL INFECTIONS

Treatment of bacterial infections should be guided by gram stain and culture, and should use doses of antibiotics appropriate to serious infections. Aspiration pneumonias can be empirically treated with IV penicillin or clindamycin; metronidazole is usually not necessary.

Urinary tract infections can be empirically treated with IV trimethoprim-sulfamethoxazole (Septra®, Bactrim®), or a cephalosporin (cephalothin (Keflin®), cefazolin (Ancef®, Kefzol®). Skin infections, such as IV site infections, can be treated with IV oxacillin or a first-generation cephalosporin.

Septic patients with no obvious source of infection can be empirically treated with a third-generation cephalosporin such as ceftriaxone (Rocephin®), cefotaxime (Claforan®), ceftizoxime (Cefizox®), or imipenem (Primaxin®). If a third-generation cephalosporin is not available, cefoxitin (Mefoxin®), cefotetan (Cefotan®) or cefuroxime (Zinacef®, Kefurox®), or a combination of antibiotics may be used to provide coverage against staphylococci, streptococci, common gram negative organisms, and anaerobes. If ceftriaxone is used, care must be taken not to inadvertently underdose by using an insufficient number of the 250 mg vials commonly supplied for treatment of gonorrhea. (A typical dose of ceftriaxone, for serious infections, would be one gram every 12 hours.)

(Use of product names is for identification purposes only, and does not imply endorsement.)

BLACKWATER FEVER (MALARIAL HEMOGLOBINURIA)

Basic treatment is bed rest. RBCs and blood volume should be restored by transfusion, however careful matching is required due to the autoantibodies already present. Both cells and plasma must be cross-matched. No special treatment of the hemoglobinuria itself is required, other than hydration.

Mild cases may require only correction of dehydration and electrolyte loss. The latter may be particularly prominent if there has been severe vomiting. However because the patient is in renal failure, care must be taken not to fluid overload the patient. In severe cases of blackwater fever, peritoneal or hemodialysis may be required.

DRUG RESISTANCE - MONITORING PARASITEMIA LEVELS

The World Health Organization (WHO) has defined chloroquine "sensitive" strains as those whose parasites are cleared from the bloodstream within seven days of the start of treatment, and do not reappear in the bloodstream for 28 days (if ever). With R-I resistance, parasites are cleared within seven days, but reappear (recrudescence) within 28 days. In R-II resistance, parasite levels fall at least 75% below their initial levels, and do so within 48 hours of the start of treatment. However the parasites are not completely cleared within seven days. R-III resistance refers to parasite levels that decrease no more than 75% in 48 hours (and may not decrease at all) and do not clear within seven days.

For most practical purposes, "resistance" to antimalarials has only been described for P. falciparum. (However chloroquine-resistant P. vivax malaria from Papua New Guinea and Irian Jaya has now been described.) An important implication of the concept of resistance is that the initial clearing of all parasites from the blood stream does not necessarily indicate the infection has been eradicated.

The level of parasitemia should be monitored by daily peripheral blood smear examinations, until no more parasites are seen.

PARASITEMIA MONITORING

Patients with complicated malaria should have the level of parasitemia determined three or four times daily, in order to monitor the response to antimalarial treatment. This should be continued until the parasite level drops significantly, or

until the patient shows significant clinical improvement. Parasitemia determinations can be reduced in frequency to once daily, when the parasitemia level falls below 3%. Peripheral blood smears should then be monitored daily until no parasites have been seen for two or three days.

All patients, regardless of infecting species, should have their level of parasitemia determined at least daily, until no more parasites can be detected in the blood. This helps to ensure the infecting species is responding to treatment, and is especially important when P. falciparum is involved. If the patient is receiving oral antimalarial agents, failure to begin to reduce parasite levels within 24-48 hours after initiation of treatment may indicate IV antimalarials are required. If the patient is already receiving IV medications, such failure may indicate the presence of a resistant strain.

A detailed method of estimating the level of parasitemia is provided in Appendix 4.

FOLLOW-UP PARASITEMIA MONITORING

Despite the fact that there are different levels of resistance, and that an initial clearing of parasites may indicate R-I level resistance rather than sensitivity, most experts do not recommend routine peripheral blood smear examinations once all parasites appear to have been cleared. Instead, the physician or independent duty corpsman should maintain a high index of suspicion, and repeat a peripheral blood smear examination if the patient clinically deteriorates or becomes febrile again.

The patient must be told that even in the best of circumstances his malaria may recur. This is most likely to occur within the next several months to a year, depending upon the species involved. However for the next several years, whenever he has an illness with a fever, and the cause is not obvious, malaria should be considered. Therefore he should tell his doctor at that time that he once had malaria.

TREATMENT OF MALARIA IN PREGNANCY

Pregnant women with malaria need prompt treatment and require careful monitoring of maternal and fetal status. No deleterious effects of quinine infusion on uterine or fetal function have been detected. Anecdotal reports that IV quinine may induce labor have not been substantiated. Even if the reports were true, this fact would be of secondary importance if the mother's life were endangered. Malaria itself is associated with

spontaneous abortions. Prompt, effective treatment of malaria may be even more life-saving for the fetus than the mother. When receiving IV quinine, uterine and fetal monitoring are mandatory. Uncomplicated cases can be safely treated with oral chloroquine, quinine, or Fansidar®.

FANSIDAR® IN PREGNANCY

Although Fansidar® is officially labeled as contraindicated in pregnancy, because pyrimethamine is teratogenic for rats, extensive use in humans has not shown indications of teratogenesis. Most authorities, therefore, consider this only a relative contraindication, and would use Fansidar® in pregnancy if clinically indicated and alternative drugs were not available or were less acceptable. When given near term, the sulfonamide component of Fansidar® may displace bilirubin in the baby, producing kernicterus.

TETRACYCLINES, PRIMAQUINE, AND MEFLOQUINE IN PREGNANCY

Tetracyclines and primaquine are contraindicated in pregnancy. Pregnant women infected with P. vivax or P. ovale should be treated with the standard chloroquine regimen, followed by weekly chloroquine prophylaxis (chloroquine phosphate 500 mg) until delivery. After delivery, or after the mother has stopped nursing, radical cure treatment with primaquine may be given. Mefloquine has not yet been approved for use in pregnancy.

NEED FOR IMMEDIATE OBSTETRICAL CONSULTATION

An immediate obstetric consultation should be obtained on pregnant women who develop malaria, so that the obstetrician is aware of the patient, and is able to evaluate her and the fetus. In most cases, little more will need to be done beyond appropriate fetal monitoring, but in some cases, Caesarean section may be life-saving to mother and/or baby.

CHILDREN AND MALARIA

Treatment in children is generally the same as adults, except for appropriate dosage adjustments. Tetracyclines are contraindicated in children under eight years of age. Life-threatening side effects associated with parenteral use of chloroquine occur more frequently and at lower doses in children. For details of the management of pediatric malaria, the reader is referred to the pediatric "Red Book," (Report of the Committee on Infectious Diseases), published by the Committee on Infectious Diseases, American Academy of Pediatrics, 141 Northwest Point Blvd, PO Box 927, Elk Grove

Village, IL, 60009-0927. The book is published every two years, generally in even numbered years.

COMMON ERRORS OF ANTIMALARIAL CHEMOTHERAPY

The following common errors are adapted from "Severe and Complicated Malaria," (Transactions of the Royal Society of Tropical Medicine and Hygiene, Vol 80 (Supplement) 1986, pp. 1-50):

- Delay in starting treatment, despite clinical suspicion of severe malaria, because the blood smear is negative or because the "drug of choice" is not available.

- Unjustified withholding of an antimalarial drug, because of exaggerated or unfounded fears of toxicity. Many antimalarial agents have greater or lesser degrees of toxicity, but malaria itself may develop complications which are life threatening.

- Dosage not correctly calculated because the patient was not weighed.

- Inadequate dosage. This is particularly true when the loading dose of IV quinine or quinidine is omitted.

- Miscalculation of the dosage because of confusion between the dose of the antimalarial agent when calculated as the salt vs calculation as the base.

- Inappropriate route of administration. The oral route is unacceptable in patients who are severely ill or have complicated malaria.

- Failure to elicit a history of recent antimalarial chemotherapy. This can result in a drug overdose, which is a particular concern when giving quinine or quinidine.

- Unjustified cessation of treatment. It is unjustified to stop quinine because a patient develops hypoglycemia or severe hemolysis with hemoglobinuria (blackwater fever), or because a pregnant woman goes into premature labor or there are signs of fetal distress. The danger of uncontrolled falciparum infection outweighs the equivocal or controllable side effects of quinine.

- Failure to control the rate of IV infusion of antimalarials. If nursing care and monitoring are inadequate, IV antimalarials may be allowed to infuse too rapidly. This may be fatal when quinine or quinidine are given.

- Failure to prevent cumulative effects of antimalarial drugs. In patients who require prolonged IV quinine for treatment, the drug may accumulate, especially when there is underlying renal or hepatic dysfunction.

- Failure to switch patients from IV to oral medications as soon as they can tolerate oral medications.

- Unnecessary continuation of IV treatment after clearance of parasitemia, or in patients with persistent coma (or other severe manifestation) despite 14 days of antimalarial chemotherapy.

- Failure to recognize that the therapeutic priorities of complicated malaria are different from those of uncomplicated malaria.

- Delay in considering obstetrical intervention in women with malaria late in pregnancy.

- Unnecessary endotracheal intubation.

- Misdiagnosis of respiratory distress. In patients with severe malaria, three serious complications - pulmonary edema, aspiration pneumonia, and metabolic acidosis - may be confused clinically.

- Failure to control convulsions.

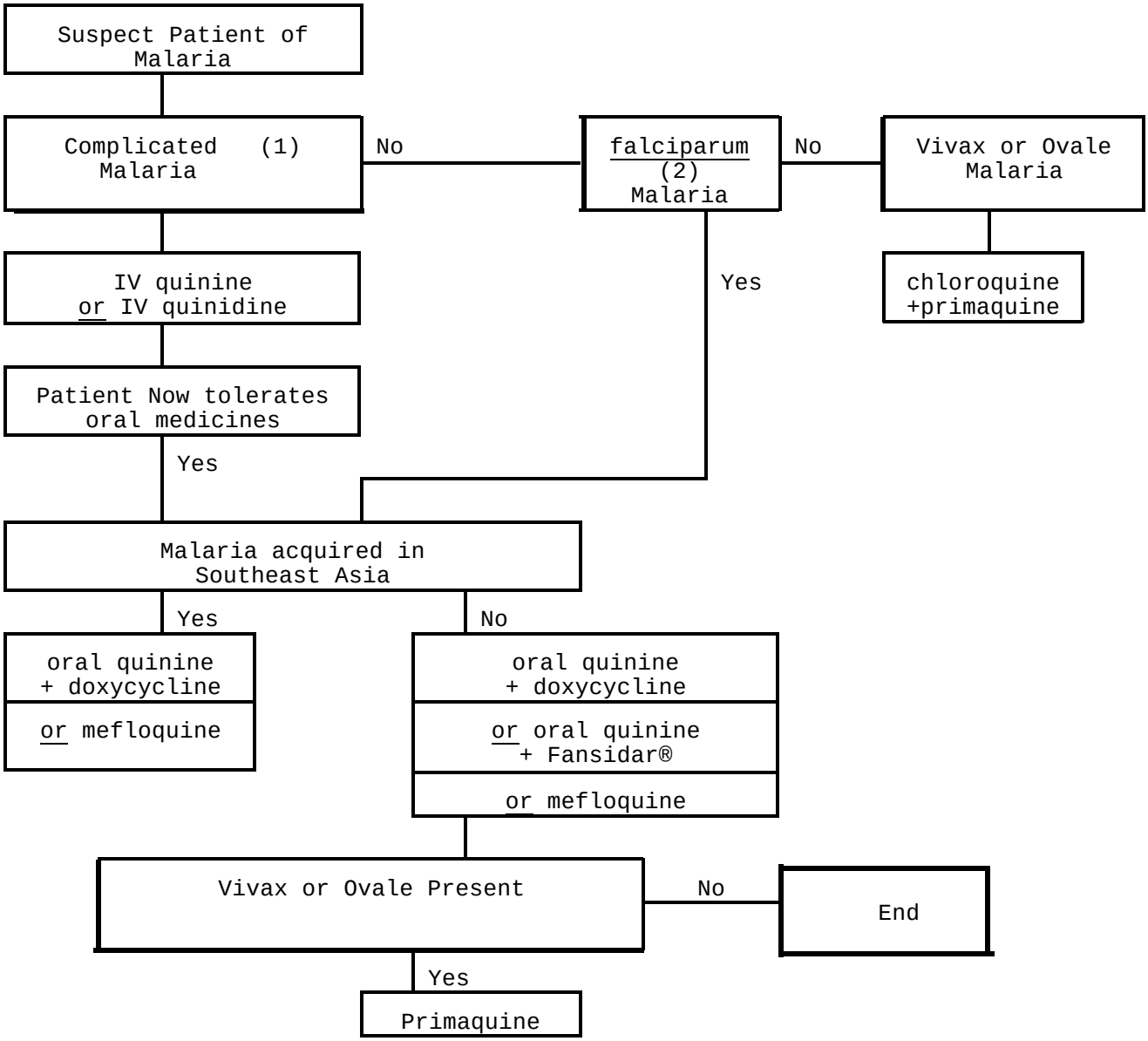
- Failure to recognize and treat severe anemia.

- Use of inappropriate and potentially dangerous ancillary therapies. There have been many fashionable ancillary therapies advocated for malaria. The following are potentially dangerous and of unproved benefit: corticosteroids, anti-inflammatory agents, osmotic agents, dextran, heparin, adrenalin, and prostacyclin.

- Delay in starting peritoneal or hemodialysis.

FIGURE 2

CHOICE OF MALARIA TREATMENT DRUG



Note: See Text for definitions and dosing regimens. Where a box provides a choice of regimens, i.e. the word "or" is used, either (or any) regimen may be used.

1. Use IV quinine or quinidine for complicated malaria due to: any malaria species (or mixed species), complicated malaria in which parasites have been seen but not identified, or complicated malaria in which no parasites have been seen, but malaria is strongly suspected.

2. Treat for uncomplicated falciparum malaria if: falciparum parasites have been seen, with or without other parasites; if parasites have been seen but cannot be identified; or if no parasites have been seen but malaria is strongly suspected.

TABLE 5

MALARIA TREATMENT REGIMENS

DRUG	DOSE	COMMON SIDE EFFECTS	REMARKS
chloroquine phosphate 500 mg (= 300 mg chloroquine base)	2 tablets initially, followed by 1 tablet 6 hours later (day 1); 1 tablet day 2; 1 tablet day 3; total dose = 5 tablets	GI disturbance.	Take drug with meals or at bedtime to reduce GI upset.
doxycycline	100 mg p.o., b.i.d for 7 days	GI disturbance. Photosensitivity.	Will also need quinine sulfate.
Fansidar® (25 mg pyrimethamine + 500 mg sulfadoxine)	3 tablets taken at one time	Allergy to sulfa.	Will also need quinine sulfate.
mefloquine	1000-1500 mg p.o. taken at one time	See text.	Dose should be adjusted for patient's weight.
quinine dihydrochloride	intravenous	See text.	See text. Requires follow-on therapy.
quinidine gluconate	intravenous	See text.	See text. Requires follow-on therapy.
quinine sulfate	650 mg, p.o., t.i.d	Cinchonism.	Duration depends on location where malaria acquired. Will also need doxycycline or Fansidar®.
primaquine phosphate 26.3 mg (= 15 mg primaquine base)	1 tablet daily for 14 days; total dose = 14 tablets	GI disturbance. Hemolysis in G6PD deficient persons.	Indicated only for radical cure of vivax or ovale malaria. Use with caution in G6PD persons (See text).
OR	3 tablets once a week for 8 weeks; total dose = 24 tablets	Same.	Same.
Only chloroquine and quinine are approved for use in pregnancy. See text.			

CHAPTER SIX

MALARIA PREVENTION AND CONTROL IN THE MILITARY

INTRODUCTION - GENERAL CONSIDERATIONS

Malaria in man results from a close environmental relationship with infective mosquitoes. Its prevention is possible by preventing infective mosquitoes from contacting man, and by interrupting the parasite's life cycle. In man, this requires the use of drugs, and repellents, and in mosquitoes, insecticides.

Effective malaria control includes four preventive measures: 1) Control of adult mosquitoes, 2) Control of larval mosquitoes, 3) Personal protection measures, and 4) Chemoprophylaxis. In tactical situations, only personal protection measures and chemoprophylaxis can be relied upon for malaria prevention, since vector control is usually not practicable. However, whenever possible, vector control should be used to the maximum extent permitted by a given situation.

For the most effective malaria prevention program, detailed information as to the risk of malaria in any given country is essential. It is not sufficient to know that a country "has malaria," since the presence, absence, or intensity of malaria risk can vary markedly within a given country. Urban areas, for example, often have no malaria risk, even though the rural areas may be at high risk. Such information has important implications for a ship going into a liberty port. Chemoprophylaxis may not be required at all for crew members who only go on liberty in the port city itself, but may be essential for the crew member who takes leave for a trip into the rural areas. Desert areas rarely have malaria, but it may be present focally in river valleys, salt marshes, and in irrigated areas. Seasonal changes, chiefly the amount of rainfall, also promote, or hinder, the mosquito vector population. In countries with mountains or uplands, there is often no malaria above a certain altitude, which varies from country to country, even though lower areas may have extensive amounts of malaria.

NAVENPVNTMEDUs

The best sources for the information needed to make informed decisions about a malaria prevention program, or to help decide if a patient presenting himself in sickbay may have been exposed to malaria, are the Navy Environmental and Preventive Medicine Units (NAVENPVNTMEDUs). These four units are located in San Diego, CA; Pearl Harbor, HI; Sigonella, Italy; and

Norfolk, VA. Detailed information as to how to contact them is in Appendix 9. A major duty of the NAVENPVNTMEDUs is to collect, analyze, summarize, and disseminate current, detailed information about the risk of malaria (and other diseases of operational concern). Such information can be obtained by contacting any NAVENPVNTMEDU directly. However it is also summarized in the Disease Risk Assessment Profile (DISRAP), which is compiled on each country, and updated every six months. Hard copies can be obtained from any NAVENPVNTMEDU, however the information can also be copied onto floppy disks, (which you must provide), which can be reviewed as needed on the Medical Department's shipboard computer.

CHAPTER SEVEN

CHEMOPROPHYLAXIS

INTRODUCTION

In the past, "chemoprophylaxis" almost always meant the use of chloroquine, with or without primaquine at the end of the prophylaxis period ("terminal prophylaxis"). During the Vietnam War this concept resulted in the development of the "C-P tab," which combined a fixed amount of chloroquine and primaquine in a single tablet, to be taken weekly. Today, when most malarious countries have, or may have, chloroquine-resistant P. falciparum malaria, chloroquine might be considered obsolescent for prophylactic purposes. Certainly its use for chemoprophylaxis requires careful consideration and advice. However alternative drugs may have a greater incidence of side effects, and, in some cases, parasite resistance.

Several chemoprophylactic regimens are included in this guide. These are the ones generally recommended by U.S. military and civilian authorities. Variations of these regimens are frequently recommended by non-U.S. tropical medicine experts who reside in, or deal with, malarious countries. In order to choose the most appropriate regimen, and because parasite resistance patterns and other variables frequently change, the cognizant NAVENPVNTMEDU or other competent authority should be consulted for the most current recommendations.

This chapter discusses several drugs commonly or potentially used for prophylaxis. For additional information, the reader is referred to Chapter 10, "Pharmacology of Antimalarial Agents." In general, most regimens begin shortly before deployment into a malarious area, continue while in the malarious area, and continue further for some weeks after leaving the malarious area. During this last period, after leaving the malarious area, primaquine is often added to eradicate certain forms of P. vivax and P. ovale which would otherwise persist in the liver (hypnozoites). Most regimens are based upon a once a week dosing schedule. Doxycycline, taken daily, is an exception.

* Figure 3, "Choice of Malaria Chemoprophylaxis Drug," diagrams the key factors in determining an appropriate drug for this purpose. It is located at the end of this chapter.

* Table 6, "Malaria Chemoprophylaxis Regimens," summarizes the drugs and doses used. It is located at the end of this chapter.

WEEKLY DOSE SCHEDULE - CHOICE OF DAY

When the once weekly dosing schedule is used, compliance can be increased by picking a day of the week which is clearly different from the other days of the week, and using that day to administer the weekly chemoprophylactic. The association of a unique day with taking chemoprophylaxis medicine helps to establish a habit pattern, which promotes compliance. For obvious reason, Sunday is a traditional choice. During military exercises or in combat, there may not be one particular day of the week which is clearly different from the others. In this case, arbitrarily picking a day, and reminding people of this through the Plan of the Day, at morning muster, and in other ways, is a suitable substitute.

CHEMOPROPHYLAXIS AND IMMEDIATE DEPLOYMENTS

Not infrequently, operational or other considerations will dictate that personnel deploy immediately into malarious areas. The usual lead time to begin chemoprophylaxis, especially the one to two weeks recommended for chloroquine, may not be available. In the rush to deploy, chemoprophylactic medications may be overlooked, or administering them to deploying personnel may be postponed. Under these circumstances, chemoprophylaxis should be started as soon as practicable, and continued on its usual schedule. (Doubling medication doses, or other maneuvers, does not overcome the delay, and is likely to reduce unit effectiveness due to more intense side effects.) In most cases, beginning chemoprophylaxis upon entry to a malarious area, when unavoidable, should not significantly increase the number of malaria cases a unit may acquire. However during emergent deployments, every effort must be made to begin chemoprophylaxis as soon as practicable. In no case should a delay in starting prophylaxis be used as an excuse to omit it altogether.

PROPHYLACTIC DRUGS

CHLOROQUINE

Three malaria species - P. vivax, P. ovale, and P. malariae - are generally considered to be chloroquine-sensitive. (Chloroquine-resistant P. vivax has been reported from Papua New Guinea and Irian Jaya.) Therefore the question of chloroquine resistance arises primarily when dealing with P. falciparum. A few areas of the world continue to have chloroquine-sensitive P. falciparum. These include Central America north and west of the Panama Canal, Haiti, and the Dominican Republic. In the Middle East these include Turkey, Syria, Egypt, Iraq, the United Arab Emirates (UAE), and Saudia

Arabia. In these areas, or in areas where only non-falciparum species are of concern, the commonest chemoprophylactic regimen is one 500 mg chloroquine phosphate tablet (300 mg base) weekly.

This should be started one to two weeks before entry into the malarious area. The early start is said to allow sufficient time for adequate blood levels to develop. However there is little evidence this practice is really necessary. Of more practical use, this period may allow the unusual individual who cannot tolerate chloroquine, or has significant side effects from it, to be identified. Appropriate steps can then be taken to deal with the side effects, or, very rarely, stop the chloroquine. By far the commonest side effect is mild gastrointestinal upset. This can usually be overcome by taking chloroquine with meals or at bedtime. If the individual really cannot tolerate chloroquine at all, mefloquine or doxycycline may be alternatives.

Chloroquine should be taken for four weeks after leaving the malarious area. Recommendations as to how long chloroquine should be continued during this period vary among different authorities. The World Health Organization (WHO) and the Centers for Disease Control (CDC) customarily recommend only four weeks. Other authorities recommend longer times.

The possible return to a malarious area must be considered in determining when to begin the terminal prophylactic regimen. If personnel are to return to the same, or a different, malarious area within four weeks after leaving the original area, weekly chloroquine should be continued until they leave a malarious area for the final time. At that point, the final four week period of prophylaxis should begin.

CHLOROQUINE-PRIMAQUINE (C-P) COMBINATION TABLETS

Each C-P tablet contains chloroquine phosphate 500 mg (300 mg base) and primaquine phosphate 78.9 mg (45 mg base). It is available only in the military supply system, and comes as a large plain orange tablet, individually wrapped in aluminum foil. It is made by Winthrop, and the aluminum foil is printed with appropriate identifying information. C-P tablets offer convenience, and may be better tolerated because they contain a buffer to reduce stomach upset. However, there are few opportunities to use C-P combination tablets nowadays.

DOXYCYCLINE

Doxycycline has been used for chemoprophylaxis during several military exercises in Thailand, due to the presence of chloroquine-resistant P. falciparum. The regimen used 100 mg

daily, beginning one or two days prior to entering the malarious area, continuing daily while in the malarious area, and further continuing daily for 28 days after leaving the malarious area. One C-P tablet was given weekly for six weeks as part of the terminal prophylaxis.

Doxycycline was fairly well tolerated, and seemed to work well. There were several complaints of stomach distress, however these were reduced by taking doxycycline with meals. Several cases of vivax malaria occurring after the exercise were reported, however these were felt to be due to poor compliance in taking primaquine, rather than resistance to the doxycycline. It is worth noting, however, that P. vivax seems to be less susceptible to doxycycline than is P. falciparum.

The potential effect, if any, of prophylactic doxycycline on travelers' diarrhea, or gonorrhea, has not been determined. It is possible that travelers' diarrhea, when it develops in individuals taking doxycycline prophylactically, may be due to bacteria which are resistant to tetracyclines, as well as other antibiotics. It is also possible that if such individuals are sexually active, they may acquire a gonococcal infection which has no symptoms, but which can be spread to other sex partners.

For the indefinite future, it is likely doxycycline will be the drug of choice within the Navy and Marine Corps for mass chemoprophylaxis against chloroquine-resistant P. falciparum malaria. It is not the ideal drug, but it seems to work, is reasonably well tolerated, and is far cheaper than the only other drug likely to be used, mefloquine.

The length of time doxycycline can be taken for prophylaxis is not known. Initial trials were limited to one month, however, it has been used by large numbers of individuals, in several exercises, for at least two months, (one month exposure plus one month terminal prophylaxis). It has been used to a lesser extent for even larger periods. None of these experiences has been associated with any unusual or severe side effects. In addition, thousands of individuals have taken tetracycline or minocycline, in doses comparable to malaria prophylaxis doses, for periods of months to years control acne. All these factors strongly suggest that prolonged use of doxycycline should be safe.

FANSIDAR®

Fansidar® is a fixed combination tablet containing 500 mg of sulfadoxine and 25 mg of pyrimethamine. For several years in the early 1980's, a regimen of one weekly tablet was used as an alternative to chloroquine as prophylaxis against chloroquine-resistant P. falciparum. Reports of Fansidar®-associated

severe skin and mucous membrane reactions began to appear, including numerous cases of Stevens-Johnson syndrome. Several of these cases were fatal. The overall frequency of severe skin reactions was felt to be about 1 in 20,000. Most of the cases had no previous history of allergic reactions to sulfonamides (or pyrimethamine). Cases seemed to occur with the intermittent dosing schedule used for prophylaxis, and not when Fansidar® was used only for acute single dose treatment of malaria. However some cases occurred after only a few doses of Fansidar®. Moreover, deaths have been reported when single doses of Fansidar® were used for treatment of meningococcal disease and cholera. For these reasons, (and more recently, because some areas report resistance to Fansidar®), Fansidar® is no longer recommended for malaria chemoprophylaxis, with rare exceptions.

Fansidar® For Presumptive Treatment of Malaria

There is a distinctly different way of using Fansidar®, which remains in effect. This is the use of Fansidar® for the acute treatment of a febrile illness which may be due to malaria, in a setting in which medical care is not readily available. The dose, for this purpose, is three tablets taken all at once. This use of Fansidar® is not prophylaxis. It is presumptive treatment of malaria. It should not be used when medical treatment is readily available, roughly, within 12 to 24 hours. Persons given Fansidar® for this purpose must thoroughly understand: a) Other diseases besides malaria may be causing the fever, and b) Even if the fever is due to malaria, the Fansidar® may not cure it. Fansidar®, used in this fashion, must be looked upon as a way to buy time until the febrile episode can be evaluated by qualified medical personnel. This must be done even if the fever goes away and the person feels better, since this effect may only be temporary.

MEFLOQUINE (LARIAM®)

Mefloquine is related to quinine and quinidine, but is somewhat more active than either of those two agents against malaria parasites. A major advantage is its extremely long half life, which allows it to be given as a single dose for treatment, or once-a-week for prophylaxis. It is active against quinine-resistant P. falciparum, however some resistance to mefloquine has already appeared, notably in Indochina.

When used for prophylaxis, the commonest side effect of mefloquine has been vomiting, which occurred in 3% of individuals. Dizziness, syncope, and extra systoles were seen less than 1% of the time. Comparison studies of mefloquine and

chloroquine, used for prophylaxis, have demonstrated that the types and frequencies of side effects are comparable for the two drugs.

The standard regimen is based on a single 250 mg tablet, given on a weekly basis. The first dose is given two weeks before entering a malarious area, the drug is continued weekly while in the area, and then continued for four additional weekly doses once out of the malarious area. At this time, there is debate over the need for a loading dose. Military investigators have shown that steady state mefloquine plasma levels are reached in 7 weeks with weekly mefloquine. Protective levels are achieved in 5 weeks. A 3-day loading dose (250 mg/day) may be considered for persons who do not have time to receive the recommended two weeks of mefloquine or will face intense transmission soon after arrival.

It is important to realize that the manufacturer's package insert does not discuss a loading dose. However, the Armed Forces Epidemiology Board (AFEB) supports the use of an alternate regimen of mefloquine prophylaxis using three daily loading doses when there is demonstrated need for rapid protection and geographic concerns about relative drug resistance. Medical providers should consult with epidemiologists at a NAVENPVNTMEDU before prescribing mefloquine loading dose regimens.

In many respects, mefloquine may be the ideal drug for prophylaxis. However resistance is already developing, and it is a very expensive drug.

PRIMAQUINE

In areas of the world where P. vivax and P. ovale species are present, terminal prophylaxis with primaquine may be necessary. ("Terminal" refers to the fact that the primaquine is not taken until after the individual leaves the malarious area.) These two species have stages which persist in the liver, hypnozoites. Chloroquine, and most other antimalarials, are not active against hypnozoites, and therefore primaquine must be given to eradicate them. If this is not done, there is a considerable risk the malaria will relapse weeks to months later, when more parasites enter the blood stream from their liver reservoir.

If primaquine is felt to be needed, it should not be started until after the individual has left the malarious area for a final time, and will not return to a malarious area. That is, the individual has begun the terminal prophylaxis phase of whatever drug he has been taking. Primaquine can be started at any time after leaving the malarious area, but must at least

partially overlap the terminal weeks when chloroquine, doxycycline, or mefloquine is taken.

There are two regimens for administering primaquine:

- One primaquine tablet daily for 14 days. (Each tablet contains 26.3 mg primaquine phosphate, equivalent to 15 mg primaquine base.) The total dose is 14 tablets.

- Three primaquine tablets once-a-week for eight weeks. (Each tablet contains 26.3 mg primaquine phosphate, equivalent to 15 mg primaquine base). The total dose is 24 tablets.

All medical department personnel must read Chapter 11, "Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency," prior to administering primaquine to any military or civilian personnel.

Each regimen has advantages and disadvantages. The 14 day daily primaquine regimen has the advantage of being short and simple - one tablet a day for two weeks. It has two disadvantages. Some people incorrectly assume that the 14 day regimen is a "short cut," and stop taking the last doses of chloroquine, or other medicine, after finishing the 14 days of primaquine. Second, daily primaquine may cause significant hemolysis even in individuals with a mild degree of G6PD deficiency.

The three tablets, once-a-week, regimen can conveniently be piggybacked onto an ongoing once-a-week regimen, such as chloroquine or mefloquine. The disadvantage of the three tablet, once-a-week regimen, is that it is a somewhat awkward regimen. It adds additional tablets at a time when compliance may be decreasing due to having left the malarious area. Compliance also may lapse because the eight week primaquine regimen extends longer than the four week terminal prophylaxis phase of mefloquine, chloroquine or doxycycline.

Glucose-6-phosphate (G6PD) Status

The G6PD status of any individual who is to receive primaquine must be known prior to administering this drug. In general, individuals with any degree of G6PD deficiency should not receive primaquine for malaria chemoprophylaxis. (See below for additional details.)

G6PD Normal Individuals

In G6PD normal individuals, the primaquine regimen of choice will generally depend upon the drug first used for prophylaxis. If doxycycline or mefloquine is used, the 14 day daily

primaquine regimen is preferred so that all medicines - doxycycline or mefloquine, plus primaquine - are completed within a month. There is limited evidence that adding weekly primaquine to daily doxycycline results in increased cases of late vivax malaria. This is presumably due to decreased compliance in taking primaquine, particularly in the weeks after terminal prophylaxis with daily doxycycline has been completed. When the primaquine was given daily, along with the daily doxycycline, prophylactic failures were not reported.

G6PD Deficient Individuals

With some exceptions, individuals who are G6PD deficient should not receive primaquine for malaria chemoprophylaxis. Instead they should be counseled that they are at some risk for developing malaria (if they were exposed to P. vivax or P. ovale) weeks to years after they leave the malarious area. They should be told of the signs and symptoms which may indicate malaria, and advised to consult a physician if such signs and symptoms do develop. They should be further counseled to be sure to tell the physician evaluating them that they were exposed to malaria.

Under certain circumstances, individuals who are G6PD deficient may need to receive primaquine for terminal prophylaxis. Whenever possible, the anticipated situation and possible need for this course of action should be discussed with epidemiologists at a NAVENPVNTMEDU, or an infectious disease or tropical medicine specialist. If primaquine is prescribed, the individuals receiving it must be counseled as to the possibility of primaquine causing a hemolytic crisis, the signs and symptoms suggestive of this, and the need to seek medical attention promptly if they develop such signs and symptoms. Traditionally, when G6PD deficient individuals have been prescribed primaquine, a weekly schedule has been used. The rationale was that a weekly regimen was less likely to produce a severe, possibly life-threatening, hemolytic crisis. However evidence that this is so, is lacking.

Primaquine prophylaxis for G6PD deficient individuals may be appropriate when: a) An individual will undergo a high level of exposure to malaria, and/or may be continuously exposed to malaria for longer than 30 days, b) An individual will be in a sustained combat situation, or c) Required in exceptional circumstances for selected individuals.

DOCUMENTATION OF PERSONAL MALARIA PREVENTION COUNSELING

All individuals who are placed on malaria chemoprophylactic agents should be carefully and thoroughly instructed as to why the medicine is being prescribed for them, how it is to be

taken, the possible side effects, and the fact that chemoprophylaxis reduces the chances of becoming infected, but is not a guarantee against infection. Personnel should also be instructed to report to the Medical Department immediately if any signs or symptoms suggestive of malaria develop. (See Chapter 4, "Diagnosis, Clinical Presentation, Clinical Course," to review signs and symptoms.) Instructions must also be given regarding the proper use of personal protection measures such as the use of DEET, permethin, and mosquito netting. (Personal protection is covered in Chapter 8 "Malaria Personal Protection Measures.")

The chemoprophylactic agents prescribed, and the instructions given, should be documented in each individual's medical record, on a Standard Form 600 (SF 600). Standardized pre-printed SF 600's may be used for this purpose. An example is given in Appendix 7.

WILSON-EDESON (W/E) TEST FOR CHLOROQUINE COMPLIANCE

During the Vietnam War, questions were raised as to whether malaria cases were due to failure of the medication to prevent malaria, or failure of the troops to take chloroquine. Verbal statements by an individual that he was taking chloroquine were not considered reliable. Therefore the U.S. Army adapted the Wilson-Edeson (W/E) test for field use, in order to detect units whose compliance with malaria chemoprophylaxis was poor. The W/E test measures chloroquine in the urine. A negative test suggests that an individual may not have been taking chloroquine, and therefore any malaria which develops may not be due to drug resistance on the part of the parasite.

The W/E test is approximately 85-90% reliable in determining the presence of chloroquine in the urine. Because of this, a negative test for any given individual cannot be taken as evidence that individual has not been taking chloroquine. This limitation has important implications if disciplinary action is being considered against an individual for not taking chloroquine. A positive test, which shows chloroquine in the urine, means he/she has been taking the drug. However a negative test, i.e. no evidence of chloroquine in the urine, does not prove an individual has been omitting his/her chloroquine.

Although of limited usefulness in individual cases, the W/E test is useful in monitoring unit compliance with chemoprophylaxis, and in fact is the only method available to do so. Approximately 10% of a unit should be monitored each week. If the number of positive tests is much below 85-90%, this suggests that a number of individuals in the unit are not taking chloroquine prophylaxis.

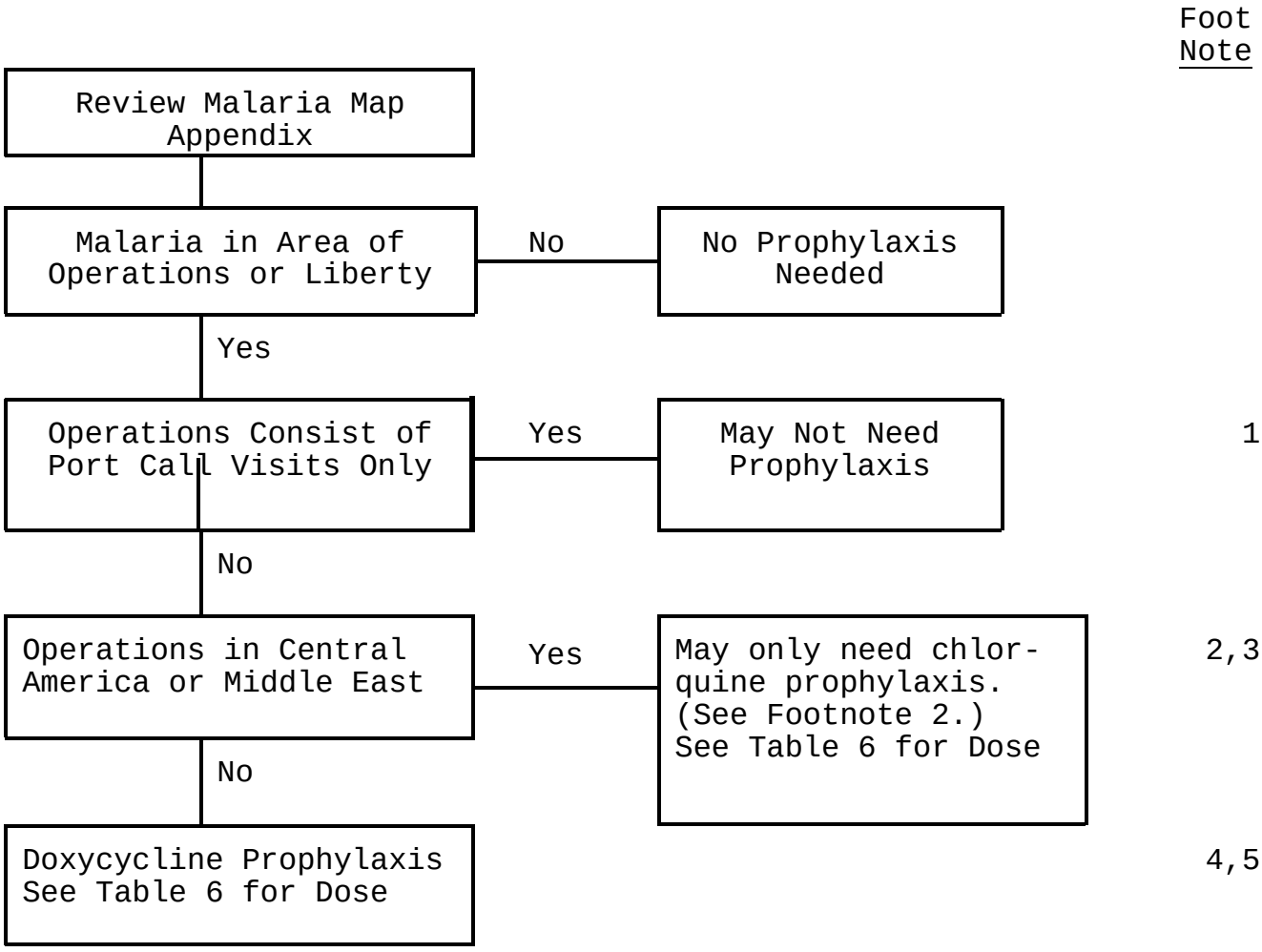
The W/E test should also be used prior to treating any case of malaria. Documented malaria, in the presence of urinary chloroquine, may indicate a chloroquine-resistant strain. If the patient's W/E test is negative, it provides no information as to whether the malaria strain is resistant or sensitive to chloroquine.

The W/E test is totally field portable. Medical personnel assigned to the Fleet Marine Force, Construction Battalions, and amphibious ships should become familiar with it and use it whenever applicable. Appendix 5 provides details of the test procedure and a list of required test supplies.

However, the W/E test is only useful for chloroquine. There are no comparable field tests for other anti-malarial agents.

FIGURE 3

CHOICE OF MALARIA CHEMOPROPHYLAXIS DRUG



MALARIA CHEMOPROPHYLAXIS ALGORITHM - FOOTNOTES

1. The map provides an overview of the most important areas of the world with malaria. Some areas with minor risk may not be represented, and the degree of risk and chloroquine resistance may vary within a given country and with time. For the most up-to-date information on specific countries and specific parts of countries, consult the nearest NAVENPVNTMEDU, or a DISRAP.

2. The following countries have chloroquine-sensitive P. falciparum: Central America north and west of the Panama Canal, Haiti, and the Dominican Republic. Middle East = Turkey, Lebanon, Syria, Egypt, Israel, Jordan, Iraq, Bahrain, Qatar, the United Arab Emirates (UAE), and Saudi Arabia. (Some of these countries have no malaria, and require no prophylaxis.)

3. If P. vivax or P. ovale malaria is common, terminal prophylaxis with primaquine or chloroquine-primaquine (C-P) tablets is indicated for all individuals who are G6PD normal. Table 6 provides the dose. Terminal prophylaxis with primaquine is not generally indicated for individuals who are G6PD deficient. (See Chapter 11 for details.)

4. Mefloquine may be substituted for doxycycline if available. See Table 6 for the dose.

5. If P. vivax or P. ovale malaria is common, terminal prophylaxis with primaquine is indicated for all individuals who are G6PD normal. The 14 day regimen may produce better compliance in taking primaquine. Primaquine prophylaxis is not generally indicated for individuals who are G6PD deficient.

TABLE 6

MALARIA CHEMOPROPHYLAXIS REGIMENS

DRUG	DOSE	COMMON SIDE EFFECTS	REMARKS
chloroquine phosphate 500 mg (= 300 mg chloroquine base)	1 tablet weekly: begin 1-2 weeks before entering malarious area, weekly while in area, then 4 weekly doses after leaving the area	GI disturbance.	Take drug with meals or at bedtime to reduce GI upset. Usefulness largely limited to parts of Central America & the Middle East.
chloroquine-primaquine (C-P) tablets	1 table weekly for 8 weeks after leaving the malarious area	GI disturbance. Hemolysis in G6PD deficient persons.	Use for terminal prophylaxis only. Substitute combined C-P tablet for separate chloroquine & primaquine tablets. Generally not to be used by G6PD deficient persons.
doxycycline 100 mg	1 tablet daily: begin 1-2 days before entering malarious area, daily while in area, continue 28-30 days after leaving area	GI disturbance. Photosensitivity.	Take with meals to reduce GI upset. Use sun protection.
Fansidar® 25 mg pyrimethamine + 500 mg sulfadoxine	3 tablets taken all at once	Allergy to sulfa.	Not for routine prophylaxis. Take tablets when febrile and medical help is not readily available.
mefloquine 250 mg	1 tablet weekly: begin 2 weeks before entering malarious area, weekly while in area, then 4 weekly doses after leaving the area	GI disturbance.	Not for use by individuals taking beta-blocker agents, flight personnel.
primaquine phosphate 26.3 mg (= 15 mg primaquine base)	3 tablets once a week for 8 weeks after leaving malarious area; total dose = 24 tablets	GI disturbance. Hemolysis in G6PD deficient persons.	Use for terminal prophylaxis only. Generally not to be used in G6PD deficient persons.
OR	1 tablet daily for 14 days after leaving malarious area; total dose = 14 tablets	Same.	Same.
Only chloroquine is approved for use in pregnancy. See text.			

CHAPTER EIGHT

MALARIA PERSONAL PROTECTION MEASURES

MALARIA DISCIPLINE

In many military operations, the likelihood of only a short stay in an area having a large mosquito population makes permanent vector control methods difficult or inappropriate. Under such conditions, personal protection measures may be the only source of protection against biting mosquitoes. Personal protection measures are so vital to military operations conducted in a malaria risk area that the term "**MALARIA DISCIPLINE**" is used to describe the ability and readiness of personnel to use them. The most important step in teaching malaria discipline is to make personnel aware of the seriousness of mosquito-borne diseases. The idea that "We are here to fight the enemy and not the mosquitoes," will severely hamper all efforts to prevent malaria.

It is the responsibility of area commanders and medical personnel to ensure that adequate personal protection items are procured and properly used.

Personal protection practices must receive the highest priority when preparing troops for duty in malarious areas. Classroom and field instruction in the proper use of personal protection measures are essential. Audio-visual aids on vector-borne diseases are available and can be used during predeployment briefings to assist in indoctrinating the troops in personal and unit protection measures. These videocassettes and films can be requested from Commanding Officer, Naval Health Sciences Education and Training Command, Audiovisual Library, Bethesda, Maryland 20889-5022, DSN: 295-1226 or Commercial: (301) 295-1226. A list of these aids may be found in Appendix 10.

PROTECTION BY PROPERLY WORN CLOTHING

Wearing clothing properly can help protect against biting mosquitoes. When mosquitoes are active, wear shirts with collars closed and sleeves rolled down and buttoned. Use blousing rings over pants and socks, making sure no bare skin is exposed. Another method is to tuck the bottoms of the trousers into the tops of the boots, or if boots are unavailable, pull the socks up around the trouser bottoms. Wear head nets and gloves where feasible.

REPELLENTS

Repellents offer significant personal protection from biting mosquitoes and other blood-sucking insects when used correctly. The use of repellents is one of the most effective personal protection strategies against mosquitoes. Many repellents act as contact repellents, keeping mosquitoes from biting when they touch the protective chemical with their mouthparts or feet. Some repellents may be sufficiently volatile that mosquitoes refrain from coming close to the treated surface. Repellents may be available as undiluted liquid concentrates or formulated as solutions, emulsions, creams, lotions, solid stick forms, or aerosols.

A repellent's period of effectiveness varies with environmental conditions, concentration and formulation of the active ingredient, arthropod species, and the activity of the person wearing the repellent. Repellents applied to the skin are removed by absorption, evaporation, abrasion, and perspiration. Consequently, the period of effectiveness is considerably reduced during strenuous activity, especially in warm, humid (tropical) weather. Repellents impregnated into clothing may remain effective for several weeks, but loss due to leaching of the repellent from laundering, rainfall, and perspiration may reduce their effectiveness over time.

Repellents can cause a burning/drying sensation if allowed to contact mucous membranes. **DO NOT APPLY REPELLENTS NEAR THE EYES, NOSTRILS OR LIPS**. Continued exposure to repellents in the folds of the armpit, elbow and knee may produce skin irritation under hot, humid conditions, but this possibility should not deter their use under these conditions.

REPELLENTS ARE SUPPLY ITEMS, NOT MEDICAL ONES. Supply personnel should adequately stock and maintain repellents for issue to troops. Recommendations concerning procurement of proper repellents are the responsibility of medical personnel.

APPLY ALL REPELLENTS ACCORDING TO LABEL INSTRUCTIONS.

INDIVIDUAL APPLICATION REPELLENTS

DEET Lotion

Insect/Arthropod Repellent Lotion (34% DEET), Tube, 2 oz., NSN 6840-01-284-3982. This cream is specifically developed for use on the skin and is currently the military skin repellent of choice. It is intended for use in combination with permethrin clothing application repellents. It contains 34% DEET (N,N-Diethyl-m-toluamide, active ingredient) in a controlled-release polymer base (lotion) and is packaged in a 2

fl. oz. polyethylene tube. It is more user acceptable, has less odor, and is less irritating to the skin and less damaging to plastics than the previous formulation (75% DEET liquid formulation). A single application of the new formulation can provide up to 12 hours of protection against biting mosquitoes. It is referred to as an extended-duration repellent (EDR).

DEET Liquid

Insect Repellent, Clothing and Personal Application (75% DEET, 25% Ethanol), 2 oz., NSN 6840-00-753-4963. This is the old liquid formulation, which comes in a 2 fl. oz. polyethylene squeeze bottle, that can still be used for personal application. However, it is a strong plasticizer and must be used with care since it can damage lacquer, paint and plastics (e.g., watch crystals, eyeglass lenses and eyeglass frames). It may cause skin irritation. It has a short duration of protection (three to four hours) and must be reapplied to the skin often, especially under warm, humid conditions where an application generally lasts for only one to two hours. This repellent also contains ethanol which has a low vapor pressure and is flammable. Exposure of the product to flame or excessive heat should be avoided.

APPLICATION OF SKIN REPELLENTS:

Following the label directions, dispense appropriate amounts of either repellent into the palm of the hand. Lightly rub the hands together with a washing motion and then rub the repellent on the arms, covering the arms. Carefully coat the back of the neck, ears, and the hairline with repellent. If wearing a shirt, it is important to apply repellent to the neck under the collar and, if a collar is lacking, low on the neck. If necessary, carefully apply repellent to other exposed areas of the body. Any exposed skin that is not treated is subject to insect bites.

Reapplication of smaller amounts of DEET may be necessary depending upon loss through sweating, wading in streams, exposure to rain, contact with wet foliage, etc.

INDIVIDUAL CLOTHING APPLICATION REPELLENTS

DEET Liquid

Insect Repellent, Clothing and Personal Application (75% DEET, 25% Ethanol), 2 oz., NSN 6840-00-753-4963. This formulation can be used to treat the uniform in areas where biting insects exist. Insects with piercing-sucking mouthparts, such as mosquitoes, will occasionally bite through tight-fitting or open weave clothing. Apply this formulation

directly to the outer surface of the uniform by hand, particularly at tight-fitting areas, such as across the shoulders, around the waist, the elbows, and on the seat of the trousers, the knees and lower pant legs. If necessary, apply it to the socks above the boots and to the entire surface of the socks if removing the boots before sleeping. If wearing a long-sleeved shirt, apply the repellent to the underside of the arms and under the cuff.

This repellent may be applied to the uniform until the whole 2 oz. bottle has been applied. This treatment should last up to several days if the DEET is not washed out by laundering, rain, or perspiration.

Permethrin

Permethrin Arthropod Repellent, 6 oz. aerosol can, NSN 6840-01-278-1336. Permethrin is the preferred product for treatment of the uniform and comes in several formulations including a 0.5% permethrin formulation in a 6 oz. aerosol can. It acts as a contact repellent against mosquitoes and other biting insects. It is odorless, non-irritating, and is resistant to several field washings. Use it to treat field uniforms and mosquito netting (e.g., bednets, headnets). **DO NOT TREAT UNDERWEAR OR CAPS AND DO NOT APPLY TO SKIN.**

Make all applications outdoors and in a location protected from the wind. Holding the can 6 to 8 inches from the clothing (while not being worn), spray the outer surfaces (front and back) with a slow, sweeping motion until the surface of the fabric appears moistened. There will be a slight color change, but the original color will be restored as the uniform dries. Treat the clothing (blouse and trousers) for a minimum of 30 seconds on each side and allow 2 hours (4 hours under humid conditions) to dry prior to being worn. Pay particular attention to trouser and shirt cuffs.

A single application of approximately 3/4 of a 6 oz. can should provide sufficient protection from biting insects and other arthropods for about six weeks under normal weekly field washing conditions. Use the remaining 1/4 of the aerosol to spray mosquito bed netting.

Do not expose the aerosol container to temperatures above 130°F as the can may burst.

Aerosol Application of DEET

If DEET is applied as an aerosol to clothing, the spray should only moisten the surface and not saturate the entire cloth. Spray all tight-fitting areas of the clothing (e.g.,

exposed socks, garment cuffs and neck and waistband/fly areas). Aerosol formulations of DEET are available only through open purchase sources.

PERMETHRIN TREATED UNIFORMS

Uniforms impregnated with permethrin are available to the troops by one of the three following methods:

FACTORY TREATED UNIFORMS

These are pre-treated uniforms provided through the standard supply system. At present, and for the foreseeable future, only the desert field uniform will be available through this source

SPRAYER TREATMENT OF UNIFORMS, NETTING, TENTS

Permethrin

Insect Repellent, Clothing Application, 40% Permethrin, 60% Inert, 5.1 ounce (151ml) plastic bottle, UI Bx w/12 bottles/Bx, NSN 6840-01-334-2666. This product contains 40% permethrin emulsifiable concentrate (EC) and is applied by individuals specifically trained to use this material. It can be applied on the outside of field uniforms, on bed netting, and on tentage using a 2-gallon sprayer (NSN 3740-00-641-4719) equipped with pressure gauge. The sprayer must be thoroughly cleaned and triple-rinsed with water prior to application. A pressure gauge (NSN 3740-01-332-8746, gauge, pressure, pesticide sprayer) is available with filter (NSN 4330-01-332-1639, filter, gauge, pesticide sprayer) to retrofit sprayers with pressure gauge adapter ports.

Applicators should wear personal protection equipment, including respirators, gloves, and goggles to avoid inhalation and pesticide contact to the face and skin. The repellent must be kept away from food, mess gear and water supplies.

To mix, fill the sprayer with one gallon of clean water followed by the 7-68 contents of the 5.1 oz. bottle and then another one gallon of clean water.

Agitate the mixture and bring the pressure in the 2-gallon sprayer to 55 psi. Approximately 40-55 full handstrokes are required to meet this pressure level. Required pressure can also be estimated by pumping the sprayer to maximum firmness. This pressure level should be maintained throughout the treatment process.

To treat clothing, place the uniform flat on the ground and spray the uniform from a distance of 12-18 inches using a fan nozzle. Spray for 50 seconds on each side of the shirt and trousers. Hang the uniform for 3 hours or until dry. The garment is ready to wear when dry. Mark the date of treatment on the inside of the uniform. One sprayer full of this mixture will treat approximately 8-10 uniforms, depending on uniform size. DO NOT RETREAT THE UNIFORMS - **ONE TREATMENT IS EFFECTIVE FOR THE LIFE OF THE UNIFORM. DO NOT TREAT UNDERWEAR OR CAPS.**

To treat bed netting, fold the bed netting in half, spread on the ground, and spray from a distance of 12-18 inches using a fan nozzle at 55 psi. Spray one side and then the other. Using a slow sweeping motion, spray the netting to completely cover the netting without runoff. The netting is ready to use when dry. Retreat after 1 year or 6 launderings.

To treat tentage, treat tents after they are erected. Only treat the entryways and the inside surface. Spray tentage from a distance of 12-18 inches using a fan nozzle. Using a slow sweeping motion, direct the spray to the walls and ceilings within reach to lightly moisten the surface of the fabric. Permethrin is compatible with fire retardant, mildew inhibitors, and water repellents applied to general purpose tents, Temper tents, boat screen (Arctic), and tent liners. One 2-gallon sprayer of permethrin should treat 1500 square feet of tentage. Retreat after 9 months in temperate climates and after 6 months in tropical climates.

INDIVIDUAL UNIFORM TREATMENT KIT

An individual uniform treatment kit may be made available to small groups of personnel who are specifically trained in its application and use (e.g., members of MMART, Disaster Assistance Teams, Preventive Medicine Teams, Medical Research Teams, etc.). This product contains 40% permethrin EC and is intended for individual use on the military field uniform. The kit contains enough materials to treat one complete uniform (shirt, trousers).

PERMETHRIN STORAGE CONDITIONS

DO NOT STORE PRODUCTS CONTAINING PERMETHRIN BELOW 32°F, as the permethrin will crystallize. However, the integrity of the product is restored when it is thawed, brought to ambient temperature, and, in the case of permethrin in the 2-gallon sprayer, agitated until all the crystals re-dissolve. The flash point of 40% permethrin EC is 115°F due to the flammable solvent used in the formulation. Storing permethrin in an enclosed space at or above 115°F may increase the chance of explosion due to ignition of vapors.

INSECT REPELLENT MESH JACKET

Parka, Fabric Mesh, Insect Repellent, NSN 8415-01-035-0846 (small), NSN 8415-01-035-0847 (medium), NSN 8415-01-035-0848 (large). Repellent-treated parkas (jackets) provide protection with a high degree of troop acceptability. The military product is a waist length mesh jacket with a hood, designed to cover the head and combat helmet, and extra-long sleeves (Figure 4). The fabric is a polyester netting (3 mesh/cm) inter-woven with cotton strands, which makes the jacket durable, lightweight (130 gm/jacket) and cool. It should be worn over outer clothing after treating it with a full 2 oz. bottle of 75% DEET (NSN 6840-00-753-4963). One bottle of 75% DEET liquid formulation is supplied with the jacket, but subsequent bottles must be procured separately. The jacket is stored in a plastic ziplock bag when not in use to retain the jacket's repellency. If properly stored and the DEET is not washed out, the repellent jacket will remain effective against mosquitoes and other biting insects for approximately six weeks before another treatment with a new bottle of 75% DEET is necessary. However, protection time depends on the number of mosquitoes in the area, climatic conditions, and wearer activity.

Before wearing the jacket, the user "charges" it by pouring 2 oz. of 75% DEET repellent (one whole bottle) onto the top and sides of the folded jacket while in its plastic bag. Reseal the bag for 24 hours by pressing the interlocking sections of the bag firmly together. After the treatment period (about 24 hrs), remove the jacket from the bag and air dry it for at least one hour before wearing, or for up to 24 hours if the odor is too strong. The bag should be kept for storage and future treatment of the jacket. When the jacket is not being worn, keep it in its ziplock pouch. Proper storage will decrease vaporization of the repellent and extend the period between DEET treatments.

The jacket should be worn over an undershirt or the uniform shirt to augment the physical protection afforded by the clothing and to avoid possible skin irritation. The hood should be worn over the helmet or head, and drawn up snugly to prevent mosquito bites to the head. The extra long jacket sleeves should be worn pulled down over the hands whenever possible.

Under field conditions, the insect repellent jacket is best used at night time or when movement is minimal. When resting, it is best to draw the hands up inside the sleeves and snap the sleeves closed. Snaps will hold the sleeves at wrist length.

The repellent jacket repels insects from the face and hands without obscuring the vision of the user. Supplemental use of skin and clothing repellents may be necessary while wearing the jacket, especially where areas of the uniform and exposed skin are not covered by the jacket.

MOSQUITO BED NETS

Mosquito Bed Nets, NSN 7210-00-266-9736. Mosquito bed nets have protected man from receiving mosquito bites in tropical areas for many years and are still one of the most useful methods of personal protection. Nets are designed for bed rolls, cots, hammocks, steel beds and shelter half-tents. Insect bar frames (poles) (NSN 7210-00-267-5641) are available for use with the folding cot. Install the poles on the inside of the bed net when using cots and on the outside when using steel beds. Tuck the bed net under the mattress or sleeping bag to prevent mosquitoes from entering.

Before deploying, each individual should obtain a mosquito bed net. If necessary, obtain additional supplies of bed nets for replacement purposes. Mosquito bed netting must be stored aboard a ship/aircraft in such a location as to make it readily available upon debarkation.

Before entering a malarious area, personnel should receive hands-on training on how to properly set up their bed nets. If used properly, the bed net should not interfere with any emergency requiring a quick exit during the night. Bed nets should be in place before dusk. Establish an inspection team to ensure compliance.

The bed net should be set up in a manner to prevent contact of the net with the sleeping person. Before going to sleep, an aerosol insecticide [e.g., 2% d-phenothrin aerosol (NSN 6840-01-067-6674)] should be used to kill any mosquitoes which may be present inside the bed net. Care must be taken not to spray the insecticide on the skin or clothing. If the sleeper contacts the net during the night, mosquitoes may bite through the net. For this reason, repellent treatment of bed nets is strongly recommended. The net should be carefully inspected, and any tears carefully repaired. If repairs cannot be made, thoroughly apply DEET or permethrin to the area around the tear.

Mosquito bed nets should be treated with the permethrin aerosol clothing repellent or the hand-compressed sprayer repellent formulation previously discussed. Treatment to the point of slight wetting is recommended. The nets should be allowed to dry thoroughly before handling. Permethrin treated bed nets should retain their repellency for several months.

INSECT HEAD NETS

Insect Head Nets, NSN 8415-00-935-3130. The head net is an olive drab, fine mesh nylon screen and cover designed to be worn over the combat helmet. It also can be worn over the bare

head or a cap. When properly worn, the head net protects against biting mosquitoes, especially those that tolerate repellents.

The cloth top piece has an elastic headband on the inside that fits securely over the head gear. Its bottom hem contains an elastic cord which is attached through a steel grommet and when tied properly fits the head net snugly below the collar. It is important to ensure that the back of the head net is well below the collar. The cord has two front loops which can be fastened tightly to uniform breast pocket buttons.

For added protection, the net should be sprayed lightly with permethrin and allowed to dry thoroughly before wearing. The net also may be treated with the 75% DEET repellent by sprinkling 3 or 4 drops in the palm of one hand, then rubbing the hands together to spread the repellent, and finally rubbing the netting between the hands. This process should be repeated until all of the netting is evenly covered. It is not necessary to saturate the netting. DEET repellent should be kept off the elastic cord to avoid damage. The head net can be removed quickly, by grasping the back of the net where it rests over the collar and pulling it forward over the head. Due to its small mesh size, the head net can be very hot or may obscure vision. If it is worn while sleeping, the head net may interfere with sleep. Its use may be limited in some climates and under certain deployed conditions.

SUMMARY

The various personal protection measures available include individually applied personal and clothing repellents, treated uniforms, bed nets, aerosol insecticides, and repellents/insecticides for treatment of netting and tentage. While each of these methods helps reduce man-vector contact, none is perfect.

The user must realize that no one specific protective method exists where personal protection is concerned. For this reason, individuals need to make use of all available methods to reduce the chance of disease transmission to the absolute minimum.

CHAPTER NINE

MALARIA UNIT PROTECTION MEASURES

VECTOR CONTROL CONSIDERATIONS

Elimination of mosquitoes is the joint responsibility of each person and their military unit. It is the duty of medical entomologists and other trained preventive medicine personnel to survey for the presence of mosquitoes at campsites, determine mosquito breeding areas, establish effective vector control programs to eliminate or reduce mosquito populations, and to supervise and provide technical guidance to improve the health and well-being of unit personnel.

SELECTION OF BASE CAMPS

The following factors for malaria prevention should be addressed when selecting base camp sites:

- Terrain.
- Climate/Season.
- Duration of stay/evolution in one or several areas.
- Present mosquito breeding sites.
- Mosquito breeding potential in dry and wet seasons.
- Disease-bearing (i.e., malaria) mosquitoes present.
- Flight range of mosquitoes.
- Direction of prevailing winds.
- Proximity of natives, domestic animals or inhabited villages.

The terrain should be either unsuitable for mosquito breeding or easily rendered unsuitable by eliminating potential breeding sites. Because of the breeding habits of some anopheline mosquitoes, locating base camps near slow-flowing streams and rivers can be hazardous. It is preferable to transport raw water to base camps located far away from rivers instead of losing many man-hours due to malaria. Entomologists or other trained preventive medicine personnel are the authority for recommending advice on the degree of anopheline mosquito activity at a possible camp site.

Base camps should be located as far away as possible from native villages or towns to avoid any contact with potentially infectious mosquitoes. Where the situation permits, consolidation of troops into a single area, instead of scattering them into many separate areas, may decrease the number of man-hours and amount of insecticides needed for mosquito and malaria control. Camps having increased cases of malaria or that are thought to be at risk of malaria outbreaks will require special attention to control the spread of disease. In instances where effective control measures cannot feasibly be implemented or cannot reasonably be accomplished, consideration should be given to relocation of the camp.

Navy Disease Vector Ecology and Control Center (NAVDISVECTECOLCONCEN) or Navy Environmental and Preventive Medicine Units (NAVENPVNTMEDU) should always be consulted for recent information on malaria incidence. Entomologists or organic preventive medicine personnel should always be consulted for recent information on malaria incidence, and the prevalence of malaria-carrying mosquitoes. This information also is available in Disease Vector Ecology Profiles (DVEPs) which are distributed by the Defense Pest Management Information Analysis Center (DPMIAC), Forest Glen Section, WRAMC, Washington, DC [DSN: 291-5365, Commercial (301) 427-5365]. The information is also available from the NAVDISVECTECOLCONCENs and NAVENPVNTMEDUs, and in the Disease Risk Assessment Profiles (DISRAPs) and Vector Risk Assessment Profiles (VECTRAPS) which are distributed by the NAVDISVECTECOLCONCENs and NAVENPVNTMEDUs.

ENVIRONMENTAL CONSIDERATIONS

Great numbers of man-made mosquito breeding places may be created as a result of engineering activities and construction projects during military operations. Many of these breeding places can be easily eliminated through more controlled engineering and construction procedures. Ideally, entomologists or other preventive medicine personnel should be consulted prior to the beginning of any engineering project which impounds water and results in the creation of potential mosquito breeding sites.

Responsible area commanders should be made aware of malaria risks and unit precautions to prevent exposure to mosquitoes when operating in suspect malarious theaters. Consultation by entomologists and other preventive medicine officers with area commanders is an on-going effort.

BASE CAMPS IN MALARIA ENDEMIC AREAS

All personnel should be instructed in how to properly use personal protection methods before entering a malarious area. Strict enforcement of these practices is ultimately the responsibility of the unit commander.

Where infectious mosquitoes exist or are suspected to exist, areas outside the camp perimeter should be off-limits to all military personnel, except as the mission requires. In more permanent situations (e.g., base camps), one of the most fundamental and effective measures for controlling malaria is to use insect-proof screens (i.e., standard field screening material) for windows.

Screening materials should be issued according to priorities, such as for buildings which will protect the largest number of personnel during peak mosquito biting periods, in most cases between dusk and dawn.

In malaria risk areas, reduce troop exposure during peak biting periods to an absolute minimum. This may involve rescheduling work hours and unit formations. Restrict showers and baths to the daytime or when mosquitoes are not biting, rather than during peak mosquito biting periods, unless they can be taken within screened enclosures designed to keep out mosquitoes. Prohibit swimming and bathing after sundown.

MOSQUITO SURVEILLANCE

The basis of any effective mosquito control program is good surveillance procedures. Without reliable information on the actual presence, abundance and species composition of the mosquitoes involved, control efforts may be wasted and resources misused. It is important to use a good map to locate mosquito breeding sites (when and where water is present), and to note the location of survey traps, military personnel, native populations, etc.

Mosquito surveillance involves collecting and interpreting information to determine what mosquito species are present, and their relative numbers and sources. This information is used to determine potential hazards due to mosquito-borne diseases and to plan, implement and evaluate mosquito control programs. Navy medical entomologists should be consulted for technical assistance to establish and conduct mosquito surveillance programs.

These trained professionals will also prove invaluable for species identification. Appendix 6 provides examples of many

important Anopheles mosquito species which are known vectors of malaria.

LARVAL MOSQUITO SURVEYS

The main goals of sampling for mosquito larvae are to identify larval habitats and to assess any marked changes (i.e., decreases or increases) in larval density as a result of control measures. When conducting larval surveys, every conceivable aquatic situation should be considered as a potential mosquito breeding site. Mosquito larvae and pupae will thrive in a wide variety of habitats. They can usually be found in areas of heavy surface vegetation, where debris is allowed to accumulate, and in sites where shallow water (less than one meter) exists. In larger ponds or lakes, mosquito larvae are usually confined to the edge of the water. When surveying for mosquito larvae it is necessary to proceed slowly and carefully, since any disturbance or shadows cast on the water may cause larvae to dive to the bottom making them difficult to collect.

Anopheles larvae are normally found at the surface of the water among aquatic vegetation or floating debris. The common white enamel kitchen dipper (dipper, kitchen white, NSN 6640-00-149-1196) or plastic dipper (NSN 7730-00-149-1196) is the most useful tool for collecting mosquito larvae and pupae. A straight stick should be attached to the handle of the dipper to extend the collector's reach. The dipper should be skimmed through the water at an angle such that one side of the dipper is pressed just below the water surface, and removed before it overflows, or gently lower it at one point allowing the water to rapidly flow into the dipper.

Tapping the edge of the dipper with a solid object (e.g., a ring) will effectively keep the larvae clustered at the bottom so excess water can be poured off. Any capped vial or water collection bag (bag, water collection, NSN 6630-01-208-2382) can be used to hold collected larvae or pupae.

Sometimes mosquito larvae are found in places where use of the dipper is not feasible (i.e., spaces too small for a dipper). These may include treeholes, plants (e.g., bromeliads in Central and South America), artificial containers, puddles or hoof prints. Under these conditions, a large-mouth dropper (NSN 6530-00-422-8120) or "turkey baster" should be used to collect the larvae. Once collected, the larvae should be poured into another container (e.g., white enamel pan) for sorting.

The number of larvae collected in each dip, the number of dips, and the total number of larvae collected should be recorded to calculate the larval index, which is the mean number of larvae collected per dip. If larvae are found in a combat environment, larvicide treatment is required regardless of the index. Notes should be kept of the relative abundance of different larval stages to estimate the occurrence of future adult populations. Information from these larval surveys is vital to justify using permanent control measures, such as filling or draining.

ADULT MOSQUITO SURVEYS

Adult mosquito surveys are most frequently conducted because adult mosquitoes are easier to locate and identify. These surveys indicate the various species present and their relative abundance and serve as an excellent way to search for larval breeding places. Adult mosquito surveys also help to determine disease outbreak potential and the need for a mosquito control program, and to evaluate control methods previously used.

Sampling methods for adult mosquito populations include human/animal biting collections and landing counts, resting station collections and the use of light traps. CO2-baited light traps may be necessary, since some anopheline mosquitoes cannot be effectively monitored using light traps alone.

BITING COLLECTIONS AND LANDING COUNTS

Collecting mosquitoes as they bite is the simplest and most direct method of determining which vector and pest species feed on man. It also provides the most useful information, such as relative abundance, host preference, place and time of biting, and species composition. Mosquitoes should be collected with a battery-operated aspirator (aspirator, insect battery operated, NSN 3740-01-210-2368) or mouth suction type aspirator (insect collector, suction type, plastic, NSN 6640-00-167-9954) for a designated period of time, usually 15-30 minutes, from a standard area, such as the exposed back of a human volunteer or animal, or from both legs. Vigilance is required to insure that landing mosquitoes are aspirated before they bite. Flashlights (NSN 6230-00-264-8261) should berased to aid in night collections.

It is desirable to convert the data to "bites per man per hour" for a standard comparison. Longer collection periods are required for Anopheles species because the total number of mosquitoes present may be quite low. In this case, it may be necessary to establish a standard index based on "bites per man per night (or bites per a given number of hours)."

In malarious areas, collectors risk the chance of acquiring the disease if mosquitoes are allowed to bite. Therefore, it may be safer to use animals (e.g., water buffaloes) to attract adult mosquitoes. However, depending on the mosquito species present, this technique may not be useful. This is because some animals do not attract the mosquito species which feed on humans or may also attract large numbers of mosquitoes which do not feed on humans, making counting and identification difficult. Other methods of collecting biting mosquitoes involve using humans or animals inside separate compartments of large screened cage-traps or net-traps, which allow mosquitoes to enter, but not escape.

When mosquito populations are very high, the landing count survey should be used to assess mosquito biting activity and to make a quick check of mosquito abundance before and after chemical treatment. An index (landing rate) is obtained by recording the number of mosquitoes which land on clothing within a certain time interval (usually one minute) instead of recording those that are actually biting. Two individuals are usually needed for this method with one counting or collecting mosquitoes landing on the back of the other.

Control measures can be evaluated by comparing collection data before and after treatment. It is important to use the same "bait" (the same collector), the same time of day, and the same place (sampling station) for each collection. Thus trends in mosquito populations will be obvious and useful.

RESTING SITES

Many species of adult mosquitoes are not active during the day and may be found resting in dark, cool and humid places protected from the wind. Daytime inspection of these natural resting sites provides comparative data on the densities of adult mosquitoes. Common natural resting sites include wells, caves, tree trunks, culverts, hollow or uprooted trees, tree holes, animal burrows, spider webs, privies, bridges, overhanging banks along streams and other similar places. Cracks and crevices in houses and other human dwellings, as well as animal shelters, specifically areas close to the ceiling and floor, are often good mosquito resting sites.

Daytime inspections are particularly useful for anopheline mosquitoes. Although time consuming and, in some cases, difficult to perform, collections of resting Anopheles populations may provide a more representative sample of the whole population.

Some malaria vectors regularly rest inside human dwellings, on walls and ceilings and under roofs and eaves, furniture, etc. These mosquitoes can easily be collected with an aspirator. A flashlight is essential when collecting mosquitoes in dark areas. Mosquitoes can be readily seen if the beam of light is aimed at an angle of about 15 degrees to the surface.

PYRETHRUM SPRAY/SHEET COLLECTIONS

Spreading white sheets over the floor of human and/or animal shelters and spraying the overhead spaces above the sheets with pyrethrum or 2% d-phenothrin aerosol is an excellent way to collect adult mosquitoes. This technique effectively "knocks-down" any mosquitoes resting overhead. For best results, use this technique during the midmorning hours.

LIGHT TRAPS AND CARBON DIOXIDE (CO2) BAITED LIGHT TRAPS

Because many species of mosquitoes are attracted to lights, light traps are the most widely used method to sample adult populations. However, not all malaria mosquitoes will come to light traps. Therefore, the species of vector present must first be determined in landing collections. If it is known that the species present is attracted to light, light traps are a great labor-saving device.

New Jersey Light Trap

The New Jersey light trap (NSN 3740-00-607-0377) provides a relative index of the number of most mosquito species present. However, some species of little concern will often be taken in large numbers. Two disadvantages to the New Jersey light trap for deployment situations are the need for a 110 volt source of electricity and its size.

Solid State Army Minature Light Trap (SSAM)

A solid state Army miniature light trap (SSAM) (NSN 3740-01-106-0091) is also available for making adult collections. Patterned after the Centers for Disease Control (CDC) portable light trap, the SSAM trap uses an improved photoelectric cell for starting and stopping the light and fan, and a better rechargeable Gel cell battery (NSN 6140-00-432-0490; recharger, NSN 6130-00-629-7396) for powering the unit. Electrical alteration allows this unit to be operated using four "D" cell batteries (NSN 6135-00-835-7210). The trap can be set out at any time of the day and is automatically activated at dusk.

Light traps should be hung near wooded areas, swamps or around potential breeding sites. Areas near other sources of artificial light or areas exposed to strong wind should be avoided. Traps should be hung 5 1/2 to 6 feet above the ground and 30 feet or more away from buildings. Light traps are operated on a regularly scheduled basis (one to seven nights per week). The total number of mosquitoes collected from each of four nights per week will usually give as valid an index as the total collected for seven nights per week. It may be necessary to move the trap (e.g., just a few yards) if the number of mosquitoes collected is significantly lower than from other traps in the area.

Daily collection reports should include species, sex, and number of mosquitoes taken at each survey location. If available, information as to temperature, humidity, and degree of moonlight is also helpful. A trapping index (determined by dividing the total number of female mosquitoes by the number of trap nights) will help to analyze the changes in population density of mosquitoes in an area.

Unfortunately, light traps used alone will not attract all Anopheles mosquitoes. In this case, light trap collections must be used along with other approved methods to sample mosquito populations. Since carbon dioxide (CO_2) is one of the primary attractants which draws an adult mosquito toward its host, it is commonly used with light traps. Dry ice is the most common source of CO_2 and may be obtained through food services. Various containers (e.g., coffee can, styrofoam container, insulated can, all with a few pin holes or screen) with dry ice in the bottom can be hung above the SSAM trap to increase the mosquito catch.

REMEMBER: Light traps and adult mosquito resting collections alone are not sufficient to monitor populations of anopheline mosquitoes. Unless circumstances will not allow use of other techniques or it has been verified that the vector species to be monitored is attracted to light, they should not totally replace mosquito collections from landing counts.

MOSQUITO CONTROL MEASURES

The goal of malaria vector control is to reduce the anopheline population below the threshold required for sustained disease transmission. Control efforts are directed at stopping contact between mosquitoes and man. In instances where malaria is being transmitted, the emphasis for control should be directed towards eliminating adult mosquitoes. When possible, conduct community relation programs to promote better

understanding of malaria risks to natives and the role of the vectors in malaria transmission.

Several approved methods are available for effective mosquito control. Some of these methods include: the use of insecticides (to control the adult and larval stages of the mosquito), source reduction techniques (to eliminate mosquito breeding sites), personal and unit protection measures, and depending on the amount of time in an area, biological control methods [e.g., the bacterial pathogen, Bacillus thuringiensis israelensis (Bti); the mosquito eating fish, Gambusia spp.].

Mosquito control methods are categorized as either permanent or temporary. Classification depends upon whether the method employed attempts to eliminate mosquito breeding sites or simply reduces the present mosquito population. When conditions allow, it is most practical to eliminate mosquito breeding sites (termed "source reduction").

Breeding sites can be made unsuitable for larval development by ditching, filling in or draining water from containment areas, removing protective aquatic vegetation, increasing the rate of water flow from springs, and other actions which completely destroy mosquito breeding sites. Aside from limiting artificial water-holding containers in bivouac areas and simple ditching to provide adequate drainage, permanent control measures have a high initial cost and may require considerable time to complete. Only temporary control methods are presented below.

CHEMICAL CONTROL OF IMMATURE MOSQUITO STAGES

Treating standing water with larvicides provides temporary control of mosquitoes and is more effective than adult control techniques. However, the biting mosquito population is not immediately affected. Larviciding should only be used when troops are located (or likely to be located) in the same area for an extended period of time (i.e., more than a few days).

Solutions, emulsifiable concentrates, granules, and water dispersible powders are effective for larviciding with ground-operated or aerial dispersal equipment. Some hand-applied larvicides are available in biodegradable plastic pouches containing insecticide (tossits), or as briquettes. Tossits and briquettes can be used in areas where vegetation is dense.

Granular larvicides also are effective where heavy vegetation must be penetrated or where possible damage to crops (e.g., rice) is a consideration. Where avoiding contamination

of water is critical, nontoxic biological and chemical larvicides (available from commercial sources) may be used. Because larvicide amounts and application rates vary with the type of equipment, mosquito species, geographical area, and level of insecticide resistance, it is important to obtain the most recent recommendations from entomologists assigned to the area NAVENPVNTMEDU or NAVDISVECTECOLCONCEN.

CHEMICAL CONTROL OF ADULT MOSQUITOES

INDOOR CONTROL

Space sprays are recommended to control mosquitoes indoors when immediate "knockdown" is necessary. Space sprays are dispensed from aerosol cans or may be applied using battery operated hand-held sprayers or fuel-driven backpack sprayers. Aerosol can space sprays should be used according to the manufacturer's instructions. Unfortunately, space sprays have little or no residual effect, and must be reapplied whenever new mosquitoes enter the space.

Where frequent mosquito reentry to a space is a problem or disease-bearing mosquito species exist, residual sprays should be applied to surfaces where mosquitoes are likely to rest. Only insecticides with long-lasting effects are suitable for use as residual sprays. Where there are rough absorbent surfaces (e.g., very porous brick, wood), a suspension (made by mixing a wettable powder) is more effective than either a solution or emulsion. When resistance to an insecticide is suspected, the nearest medical entomologist should be consulted for technical assistance.

OUTDOOR CONTROL

Ultra-low-volume (ULV) spraying is the treatment method of choice to control adult mosquitoes. ULV sprays often result in complete control within a limited region and provide adequate protection for short periods. However, in any sizable area where continuous mosquito breeding is evident, ULV insecticides must be used on a repetitive schedule, typically every day or every other day. When properly applied, ULV treatments do not leave dangerous or unsightly pesticide deposits on trees, bushes or real estate.

ULV treatment operations should be conducted when wind speeds are minimal (less than 6 knots per hour) and the ground is cooler than the atmosphere directly above it (temperature inversion). Temperature inversions usually occur at sunrise or sunset. Since ULV applications are most effective against flying insects, spraying operations should occur when the

target species are active (e.g., at dusk, after dark, early in the morning, near sunrise).

BARRIER TREATMENTS

Residual spray treatments provide some protection against mosquito reinfestation when used as barrier treatments in small bivouac areas. To establish a barrier, spray all vegetation surfaces with an appropriate insecticide for a distance of 30 meters or more around the area to be protected. Insecticide dispersal can be accomplished by hand-held or backpack sprayers.

AERIAL INSECTICIDE APPLICATION

OPNAVINST/CMC 6250.4 series addresses the use of aircraft to disperse insecticides. Only certified Department of Defense (DOD) entomologists or applied biologists are authorized to approve aerial dispersal of insecticides. Qualified pest control personnel must supervise the operation. Aerial insecticide dispersal methods depend on the size of the treatment area, the amount of vegetation present [i.e., canopy (vegetative) cover] and the density of surface vegetation. Other factors which determine the use of aerial dispersed insecticides include the suitability of alternate measures to control heavy mosquito populations, the prevalence of vector-borne diseases, and the ability to increase work efficiency.

CHAPTER TEN

PHARMACOLOGY OF ANTIMALARIAL AGENTS

AMODIAQUINE

Amodiaquine is related to chloroquine, but was thought to be more effective against chloroquine-resistant P. falciparum. For this reason, amodiaquine was increasingly used in the mid-1980's for chemoprophylaxis. However in 1986, 25 cases of agranulocytosis were associated with the drug, seven of them fatal. During the same period, malaria resistance to amodiaquine increased, from 5% in 1982 to 22% in 1984, in the Philippines. For these reasons, amodiaquine is no longer recommended for chemoprophylaxis of malaria.

CHLOROQUINE

Activity

Chloroquine, a 4-aminoquinolone, is the drug of choice for treatment of acute attacks of malaria caused by the three non-falciparum species, P. vivax, P. ovale, P. malariae, and susceptible strains of P. falciparum. It is highly effective against the asexual erythrocytic forms, of these species, and the gametocytes of P. vivax. Its action is rapid and symptoms are controlled in 24 to 48 hours. Thick smears become negative in 48 to 96 hours. Chloroquine exerts no significant activity against sporozoites nor against the exoerythrocytic (liver) tissue stage of plasmodia. Therefore it does not prevent establishment of infection nor does it prevent relapses. Chloroquine prophylaxis prevents the symptoms of malaria by killing the parasites as they break out of the liver cells and into the RBCs. Once chloroquine is stopped, a subsequent infection can develop as new parasites continue to leave the liver cells. Elimination of the hepatic hypnozoites, the "reservoir" or exoerythrocytic tissue stage of P. vivax and P. ovale, requires "radical cure" treatment with primaquine.

Pharmacology

In healthy persons, chloroquine is rapidly and nearly completely absorbed from the gastrointestinal tract. However, since the mesenteric (gut) circulation may be impaired in severe malaria, gastrointestinal absorption may be reduced, making the oral route of administration unreliable. The drug is slowly excreted by the kidney, which allows the drug to be taken once a week for prophylactic purposes. Tissue levels are very high, reaching 200 to 700 times the plasma level in liver, spleen, kidney, lung, and melanin-containing tissues. In the

brain and spinal cord, levels reach 10 to 30 times that of plasma.

(Chloroquine is usually administered orally. It can be administered intramuscularly or intravenously. (See NJ White et al, J Infectious Diseases 1987; 155:192-201, for adult doses, and NJ White et al, New England J Medicine 1988; 319:1493-1500 for pediatric doses.) The parenteral form (hydrochloride salt) can be given instead of the oral phosphate salt when severe nausea or vomiting occurs, when absorption of the drug is in question, or when the infection is particularly severe. Rapid intravenous injection causes dizziness, nausea, disturbance of vision, and a transient fall in blood pressure. Oral administration should be substituted as soon as practicable. Because IV quinine or quinidine, which are effective against all four human malaria species, should always be available to Navy medical personnel, it should not be necessary to use parenteral chloroquine.)

Side Effects

Most adverse effects resulting from antimalarial doses of chloroquine are relatively mild since the dose used for prophylaxis is small and the larger doses employed to treat acute attacks are given only for short periods. Adverse effects are dose-related and include gastrointestinal discomfort with nausea and diarrhea, pruritus, rash, headache, central nervous system stimulation, and reversible interference with visual accommodation. Most gastrointestinal reactions can be minimized by administering the drug with meals.

WARNING: Overdose - Suicidal, and Accidental in Children

Acute oral overdosage of chloroquine, usually seen in suicide attempts, can cause acute circulatory failure, convulsions, respiratory and cardiac arrest, and death. Several case reports have documented the danger of young infants swallowing chloroquine tablets that are left accessible to them. Most cases end fatally or with severe neurologic sequelae due to anoxic encephalopathy. All personnel administered chloroquine should be warned about this, and the need to be certain young children do not have access to this drug. If personnel are still taking chloroquine at the time they return home from a cruise or an operation, they should be reminded of this potential problem. Treatment of chloroquine overdose is supportive, including large bore gastric lavage followed by instillation of charcoal. However chloroquine is rapidly absorbed, and further treatment with diazepam and epinephrine is often required (B Brio et al, New England J Medicine, 1988; 318:1-6).

Nomenclature

Chloroquine tablets may be referred to in either of two different ways. This results in considerable confusion as to the dose to be given, unless careful and consistent terminology is used. The standard U.S. military issue chloroquine tablet may be described either as "chloroquine phosphate, 500 mg," or as "chloroquine base, 300 mg." Both terms refer to the same tablet, which contains 300 mg of chloroquine base, the active ingredient, and 200 mg of phosphate. Together they add up to 500 mg of chloroquine phosphate. (Base chloroquine is chemically combined with phosphate so that the chloroquine remains stable while in the tablet form. In the stomach, the phosphate is dissolved off, releasing free chloroquine base which is then absorbed into the blood stream.) In the U.S. military system, chloroquine has usually been supplied by Winthrop Corporation, as a pink, film-coated tablet, with a "W" within a box on one side, and "A77" on the other. Winthrop's trade name is "Aralen."

CHLOROQUINE-PRIMAQUINE ("C-P") TABLETS

This tablet combines a fixed dose of 500 mg of chloroquine phosphate plus 79.8 mg of primaquine phosphate (the equivalent of three regular primaquine tablets). It was devised during the Vietnam War for convenient administration of malaria chemoprophylaxis. One tablet is taken weekly. C-P tablets are used for prophylaxis only, and have no place in the treatment of acute clinical malaria.

DOXYCYCLINE (SEE TETRACYCLINE)

FANSIDAR®

Fansidar® is the brand name of an antimalarial drug which combines 500 mg of sulfadoxine and 25 mg of pyrimethamine in a single tablet. A parenteral preparation for IM injection is available in many countries. Both components are well absorbed orally and are excreted mainly by the kidneys. The apparent half-life of sulfadoxine ranges from 100 to 231 hours with a mean of 169 hours. The pyrimethamine half-life ranges from 54 to 148 hours with a mean of 111 hours.

Activity

Fansidar® is usually effective for the treatment of chloroquine-resistant P. falciparum malaria. However, Fansidar® susceptibility of malaria strains varies by geographic location and the number of areas reporting resistance is increasing. Fansidar® resistance is a particular problem in Southeast Asia. Fansidar® is compatible with other

antimalarial drugs, particularly quinine, and with most antibiotics. (See comments on antifolates below.)

Contraindications

Contraindications to the use of Fansidar® include: age less than two months old, and hypersensitivity to pyrimethamine or sulfonamides. Deaths associated with the administration of Fansidar® have been reported due to hypersensitivity reactions, agranulocytosis, and aplastic anemia. In these cases the drug had been used for prophylaxis, not treatment. Pregnancy is listed in the manufacturer's instructions (package insert) as a contraindication to the use of Fansidar®. However this appears to be a relative contraindication. Several hundred women have received this drug while pregnant, apparently without ill effects.

Fansidar® should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency, and to those with severe allergy or bronchial asthma. Some sulfonamide drugs produce hemolysis in G6PD deficient individuals, although this has not yet been reported with Fansidar®. Urinalysis with microscopic examination and renal function tests should be performed during long term therapy of those patients who have significantly impaired renal function. Adequate fluid intake must be maintained to prevent crystalluria and stone formation.

Antifolate drugs such as other sulfonamides, or trimethoprim-sulfamethoxazole combinations, (Bactrim®, Septra®), should not be used while the patient is receiving Fansidar® for antimalarial prophylaxis. Prolonged administration of Fansidar® may cause folic acid deficiency. This is primarily manifested by white blood cell suppression. Such suppression mostly occurs with prolonged administration of these drugs in patients whose bone marrow is severely malnourished or who are immunosuppressed (cancer chemotherapy, AIDS), or when Fansidar® is given in combination with other antifolate drugs. It is unlikely to occur in young healthy individuals, who receive a single dose of Fansidar®.

FANSIDAR®-MEFLOQUINE (FANSIMEF®) COMBINATION TABLET

This combination tablet is available outside the U.S. Resistance to the combination has already developed in some areas of the world, notably Southeast Asia where the drug has been available for some years. It offers little if any advantage over mefloquine, and its use is not recommended.

MEFLOQUINE (LARIAM®)

Activity

Mefloquine is a 4-quinoline methanol drug, related to quinine, which was developed in response to the proliferation of multidrug resistant strains of P. falciparum. In a single dose, it eliminates fever and parasitemia rapidly in nonimmune individuals in malaria endemic areas, who are infected with either chloroquine-sensitive or highly chloroquine-resistant strains of P. falciparum. Mefloquine is also active against Fansidar®-resistant strains of P. falciparum. Mefloquine is equally effective for the treatment of acute vivax malaria, but it does not eliminate the exoerythrocytic (hepatic phase) of P. vivax. There is insufficient data to evaluate the efficiency of mefloquine against P. ovale or P. malariae.

Mefloquine comes in 250 mg tablets. Single doses of 15 to 25 mg/kg (1.0-1.5 gram maximum adult dose) given orally have been effective in curing chloroquine-resistant P. falciparum. However, resistance to this drug has recently been demonstrated or reported in Southeast Asia and west Africa. Mefloquine can also be used for the prophylaxis of P. falciparum and P. vivax malaria infections, especially in areas with chloroquine-resistant strains of P. falciparum. However it is a very expensive drug, and for this reason its prophylactic use is not generally recommended for large groups of U.S. military personnel unless cheaper drugs are not effective.

An additional benefit of mefloquine is its long half life. This allows eradication of parasites, with a single dose. Unlike treatment with quinine, additional treatment with Fansidar® or a tetracycline is not necessary. Therefore for greater efficacy and convenience, a single oral dose of mefloquine is preferred to either oral quinine or oral quinidine for treatment of malaria.

Pharmacology

Mefloquine acts as a blood schizonticide. Its mechanism of action is unknown, but is probably similar to quinine. Mefloquine is well-absorbed orally and is extensively plasma bound. Peak concentrations occur in a few hours and decline slowly over several days. Liver and lung tissue levels remain high for extended periods of time. Mefloquine has not caused hemolysis in G6PD deficient individuals.

Side Effects

Mefloquine has been studied extensively for malaria treatment, but less so for chemoprophylaxis. Toxicity appears

to be greater when the drug is used for treatment, probably because of the higher doses used. Side effects associated with treatment have been reported as occurring with the following frequencies: nausea (18%), vomiting (13%), diarrhea (15%), dizziness (15%), abdominal pain (8.3%), self-limited sinus bradycardia (9%), and neuropsychiatric changes (0.9%). Most studies have noted that it is often not possible to determine whether these effects were due to mefloquine, or to the underlying malaria. In contrast, when used for prophylaxis, the commonest side effect was vomiting, which occurred in 3% of individuals. Dizziness, syncope, and extrasystoles were seen in less than 1% of patients. Comparison studies of mefloquine and chloroquine, used for prophylaxis, have demonstrated that the types and frequencies of side effects are comparable for the two drugs.

Contraindications

Mefloquine is contraindicated for use in pregnancy, or in individuals who are concurrently taking beta-blocker drugs. Its use in individuals who are taking quinine or quinidine may produce electrocardiographic abnormalities or cardiac arrest. Its use with quinine or chloroquine may increase the risk of convulsions.

PRIMAQUINE

Activity

Primaquine is an 8-aminoquinolone. Its greatest value lies in its ability to produce a "radical cure" of vivax and ovale malaria. It does this because of its unique ability to eradicate hepatic hypnozoites, the exoerythrocytic stage. It has little or no activity against the erythrocytic stages of any species of malaria. For this reason it is almost always used in conjunction with a blood schizonticide, such as chloroquine. The 8-aminoquinolones exert a marked effect against the gametocytes of all four species of Plasmodium that infect man, especially P. falciparum. This action helps prevent the spread of malaria to others, since gametocytes are taken up by, and continue their life cycle in, mosquitoes. However, this is usually not a primary goal in treating military personnel.

Pharmacology

Oral primaquine is absorbed promptly, and then is rapidly metabolized. Plasma concentrations peak at one to two hours and then fall with a half-life of three to six hours. Little is known about primaquine's mode of action. Resistance has occurred only in experimental animal models.

Side Effects

Primaquine is usually well tolerated. Its side effects include abdominal discomfort, nausea, headache, interference with visual accommodation, and pruritus. Methemoglobinemia is common, but rarely necessitates interruption of therapy. Leukopenia and agranulocytosis occur rarely. Primaquine is contraindicated in pregnancy.

Side Effects - G6PD Deficiency

Primaquine's most serious adverse effect is intravascular hemolysis, manifested as acute hemolytic anemia in patients with some types of glucose-6-phosphate dehydrogenase (G6PD) deficiency. In healthy individuals with G6PD deficiency, the severity of the hemolysis varies directly with the dose of primaquine and the degree of G6PD deficiency in the RBCs. Primaquine may also induce hemolysis in individuals with other defects of the erythrocytic pentose phosphate pathway of glucose metabolism and in patients with certain hemoglobinopathies. Medical Department representatives who prescribe primaquine must first read Chapter 11, "Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency," to familiarize themselves with the nature of G6PD deficiency and the potential consequences of administering primaquine to those who have it.

Nomenclature

As with chloroquine, primaquine tablets may be referred to in either of two different ways, as the base or as the phosphate. In the case of primaquine, standard U.S. military issue primaquine tablets may be described either as "primaquine phosphate, 26.3 mg," or as "primaquine base, 15 mg." In the U.S. military system, primaquine is usually supplied by Winthrop Corporation, as a small, white, film-coated tablet, with a "W" within a box on one side, and "P97" on the other.

QINGHAOSU

Qinghaosu (QHS, artemisinin) is an ancient Chinese herbal remedy, currently undergoing systematic evaluation. Several studies demonstrate QHS is a notably effective antimalarial, especially for cerebral malaria. However, several years of additional work, including the development of large scale production methods, will be required before QHS is readily available.

QUININE SULFATE (ORAL FORM)
QUININE DIHYDROCHLORIDE (IV FORM)

Activity

Quinine is the major alkaloid extracted from the bark of the cinchona tree, which is indigenous to certain regions of South America. Quinine acts primarily as a schizonticide. It has little effect on sporozoites or exoerythrocytic (hepatic) forms of malarial parasites. The alkaloid is also gametocidal for P. vivax and P. malariae, but not for P. falciparum. As both a suppressive and therapeutic agent, quinine is more toxic and less effective than chloroquine. However, it is especially valuable for the treatment of severe illness due to chloroquine-resistant strains of P. falciparum.

Quinine is rapidly schizonticidal, but it has no long term effect. Therefore it must either be given for seven to 14 days, or used with a tetracycline-type drug, or with Fansidar®. Because of the side effects (cinchonism) associated with quinine, several days' use of this drug may not be well tolerated. Whenever possible, the safer and more rapidly-acting chloroquine should be used instead of quinine in uncomplicated malaria caused by non-falciparum species, or by chloroquine-sensitive P. falciparum.

Pharmacology

For oral administration, the most commonly used salt of quinine is quinine sulfate. It should be taken immediately after meals to minimize gastric irritation. It is absorbed from the upper small intestine, where absorption is nearly complete, even in patients with diarrhea. Peak levels occur one to three hours after a single dose. After termination of therapy, plasma concentrations fall with a half-life of 12 hours. CNS levels are only 2-5% of the plasma concentration.

Side Effects

The usual therapeutic antimalarial doses of oral quinine sulfate frequently cause symptoms of mild to moderate cinchonism (tinnitus, headache, altered auditory acuity, blurred vision, nausea, diarrhea), but these symptoms seldom are severe enough to require stopping treatment. Severe symptoms develop rarely with oral doses, but are a greater concern with IV administration of quinine dihydrochloride. Asthma may be precipitated in susceptible individuals. Urticaria is the most frequent allergic reaction and pruritus may develop with or without a rash. Signs of hematologic toxicity include acute hemolysis (including, rarely, blackwater fever), hypothrombinemia, thrombocytopenic purpura, and agranulocytosis. The precise role played by quinine in precipitating blackwater fever is unknown.

Rapid intravenous administration of quinine dihydrochloride may produce hypotension and acute circulatory failure. It should be injected over two to four hours or by continuous infusion. Malaria patients are sensitive to fluid overload, and may develop pulmonary edema if too much fluid is administered, especially if administered too quickly. This fact must be considered because of the relatively large doses of fluid required for administration of IV quinine. Oral administration of the sulfate salt should be substituted as soon as possible. Although less cardiotoxic than quinidine, similar cardiologic side effects may also be seen. (See "Quinidine Gluconate," "Side Effects," next Section.)

Contraindications

Quinine should be given with caution to patients who have atrial fibrillation and to those who manifest an idiosyncratic reaction to it in the form of cutaneous angioedema, visual symptoms, or auditory symptoms. This drug is contraindicated for the treatment of uncomplicated malaria in the presence of optic neuritis and tinnitus.

Availability

The IV form of quinine is available only by open purchase in developing countries. Therefore it may be difficult to obtain in emergencies. Parenteral quinine is included in certain Authorized Medical Allowance Lists (AMAL)s, but not all units have access to the appropriate AMAL. As a substitute, therapy with IV quinidine gluconate may be necessary.

QUINIDINE GLUCONATE

Activity

Quinidine has the same structure as quinine except for the stearic configuration of the secondary alcohol group. In the past few years, interest in IV quinidine for treatment of malaria has increased, primarily due to difficulties obtaining parenteral quinine. Quinidine is more active against malaria species than is quinine, and has been used successfully to treat falciparum infections which recrudesced after treatment with quinine. The doses used in various studies have been slightly less than the doses used with quinine. Although quinidine is more active against malaria parasites than is quinine, it is also about four times as cardiotoxic.

Side Effects

Prolongation of the QT interval, generally by about 24%, widening of the QRS complex, and T-wave flattening have been

frequently noted with the use of quinidine, and are associated with higher plasma levels. However, dysrhythmias have not been seen in patients receiving rate controlled infusions. Hypotension has occasionally been seen while infusing the loading dose, but the blood pressure increased when the infusion was temporarily stopped and then restarted at a slower rate. Formal research protocols have generally included monitoring of plasma quinidine levels, however studies have indicated that IV quinidine can be administered safely with only careful monitoring of infusion speed, blood pressure, and the electrocardiogram.

Other side effects and contraindications are, in general, comparable to those seen with quinine.

TETRACYCLINE, DOXYCYCLINE

Activity

This class of drugs is active against all strains of malaria, however it is only slowly effective. Therefore, its primary treatment use is in combination with other faster acting antimalarials, primarily quinine, to treat acute attacks of multidrug-resistant or chloroquine-resistant P. falciparum malaria. Tetracyclines are apparently effective against primary tissue schizonts of chloroquine-resistant strains of P. falciparum, and against the erythrocytic forms of P. falciparum and P. vivax. Doxycycline has been used in Southeast Asia as a prophylactic agent against P. vivax and chloroquine-resistant P. falciparum. It is effective, although perhaps less so against P. vivax which seems to require a higher dose of tetracycline for maximum efficacy.

Side Effects

The commonest side effects associated with the tetracyclines are nausea and epigastric distress, and, uncommonly, diarrhea and vomiting. These are seen considerably less often with doxycycline. Stomach and esophageal ulceration have been reported due to tetracycline antibiotics. Doxycycline, but not tetracycline, can be taken with meals, which greatly reduces the frequency and severity of gastrointestinal side effects. Absorption of doxycycline is not affected by food or diary products, however iron products (such as vitamins with iron), antacids (such as Maalox, or Mylanta), and Pepto Bismol all interfere with the absorption of doxycycline. They should be avoided when doxycycline is used, and patients should be told about this interaction.

Photosensitivity also occurs with doxycycline, and may be more likely in tropical areas due to longer and more intense

exposure to the sun. The commonest reaction resembles a severe sunburn on sun-exposed areas, and can be treated as such.

CHAPTER ELEVEN

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

PATHOPHYSIOLOGY OF G6PD AND HEMOLYSIS

G6PD is an enzyme in the pentose phosphate pathway (hexose monophosphate shunt) in red blood cells (RBCs), which is involved with glucose metabolism. Specifically, it catalyzes the conversion of NADP+ to NADPH, a powerful reducing agent which helps protect the cell against oxidative attack. Primaquine is a powerful oxidizing agent. RBCs which are deficient in G6PD are susceptible to oxidation by primaquine and, consequently, hemolysis.

G6PD deficiency is a sex-linked genetic disorder, with full expression in males. There are over 200 variants of G6PD deficiency. For the U.S. military, two important variants are the A- (A negative) variant, which affects approximately 10% of black American males, and the Mediterranean variant, which is the most common type affecting Caucasians. Asian variants also exist. Different G6PD variants correspond to different degrees of G6PD deficiency, which range from mild to severe. The greater the degree of enzyme deficiency, the greater the risk of causing severe damage to RBCs when they are exposed to oxidizing agents.

Persons who are G6PD deficient are at risk of experiencing hemolytic anemia when taking primaquine. Whether or not hemolysis occurs, and the amount of hemolysis if it does occur, depend on both the dose of primaquine and the individual's degree of G6PD deficiency. Chloroquine, quinine, and quinidine may cause hemolysis in individuals with the Mediterranean or Asian G6PD variants. However it is a rare occurrence. Sulfonamide-type drugs have also been associated with hemolysis in G6PD deficient individuals. However, Fansidar®, which contains sulfadoxine, has been used extensively for years, and hemolysis in G6PD deficient individuals has not been reported. As a practical matter, G6PD deficiency becomes important almost exclusively when using primaquine.

Although quantitative tests to measure the degree of G6PD deficiency are available, the routine testing of Navy and Marine Corps personnel is qualitative. It indicates whether the individual has, or does not have, G6PD deficiency, but it does not indicate the degree of deficiency. Large Navy hospitals have access to quantitative G6PD testing. In some cases, this information may be useful in making decisions as to how to treat an individual.

G6PD TEST RESULTS AND MEDICAL RECORDS

Before deploying to a malaria risk area, the medical records of all personnel should be checked to be sure G6PD testing has been done and the results entered in their medical records. This should be done far enough in advance of deployment to allow personnel who lack this information to be tested, and for the results to return to their command and be entered into their medical records. (See Chapter 12, "Navy Responsibilities in Malaria Control," Section 10, "Program Management, Medical Records," for detailed information about this topic.)

MONITORING G6PD DEFICIENT INDIVIDUALS

Monitoring of G6PD deficient persons taking primaquine prophylaxis could include a urine dip stick and hematocrit at the initiation of primaquine, at a midpoint, and upon completion of primaquine prophylaxis. Individuals with a drop in hematocrit or a positive urine dip stick for bilirubin, blood, or protein would stop taking primaquine until consultation with a medical officer is possible. Although perhaps theoretically desirable, such monitoring has never been practiced on a routine basis in the military, and its efficacy and practicability have yet to be demonstrated.

REACTION TO PRIMAQUINE IN G6PD DEFICIENT INDIVIDUALS

About 10% of U.S. Black males develop a mild anemia due to intravascular hemolysis when taking one primaquine phosphate tablet (26.3 mg primaquine phosphate, 15 mg base), daily. The hemolysis usually stabilizes, and the hematocrit then usually returns to normal with continued primaquine treatment.

A greater degree of primaquine sensitivity can be found in some darker-hued caucasian ethnic groups, including Sardinians, Greeks, Sephardic Jews, and Iranians. If such personnel who are G6PD-deficient use weekly chloroquine/primaquine tablets for over 16 weeks, they may develop a chronic anemia. Terminal prophylaxis in these individuals, using a 14-day regimen of daily primaquine phosphate, may be more likely to produce a hemolytic crisis, which could be fatal unless immediate blood transfusions are provided. However, evidence is lacking that a 14-day regimen actually carries a greater risk.

In an experimental study, a group of Blacks who were G6PD deficient were given a single primaquine tablet, either once or twice a week. Their hemoglobin levels fell 1.6-2.4 grams/dL below their baseline values, reaching a low of 12.5-13. Their hematocrit levels fell 4-7 percent, to a low of 39-41 percent. In contrast a group of Sardinians (Italians) received a single

dose of 45 mg of primaquine base. Their hematocrit values fell from a mean baseline level of 43 percent (range: 31-48) to a mean of 33 percent (range: 24-40). A second dose a few days later produced a further drop in some individuals, but not in others.

CONSIDERATIONS IN USING PRIMAQUINE IN G6PD DEFICIENT INDIVIDUALS

The use of primaquine is greatly complicated by the presence of G6PD deficiency. Primaquine is only required for P. vivax and P. ovale malaria infections, which are essentially not fatal in otherwise healthy individuals. Hemolysis, due to administering primaquine to G6PD deficient individuals, could be fatal. However development of vivax or ovale malaria after chemoprophylaxis without primaquine, or the recurrence of such malaria after treatment without primaquine to produce a radical cure, results in a loss of manpower. When large numbers of individuals, or key individuals, are involved, this could be a significant factor in an operational setting. In contrast, weekly doses of primaquine seem to be well tolerated, even by individuals who are G6PD deficient. During the Vietnam War, thousands of individuals took weekly chloroquine-primaquine (C-P) tablets; only about 20 are reported to have had a significant reaction from taking primaquine in the presence of G6PD deficiency. However the number of lesser reactions, as well as the degree of compliance in taking C-P tablets, are not known.

The problem is further complicated by the distinction between G6PD deficiency in Blacks and non-blacks. G6PD deficiency in Blacks is generally held not to be life-threatening in the presence of primaquine. Because of this, and because Blacks make up a significant proportion of G6PD deficient individuals in the Navy and Marine Corps, it might be desirable to manage G6PD deficiency in these individuals differently than in non-blacks. For example, Blacks who are G6PD deficient could be administered primaquine on a weekly basis, whereas non-blacks who are G6PD deficient could omit primaquine. However the presence of two different prophylactic regimens tends to promote confusion, and decreased compliance in taking primaquine (or C-P tablets). Recently, the Air Force reported one case of a Black male who developed a severe hemolytic anemia while taking weekly primaquine. The assumption that Blacks always have a mild degree of G6PD deficiency may not be fully accurate.

There is also a medicolegal consideration. Although the Vietnam experience would seem to indicate that weekly C-P tablets had an acceptably low incidence of side effects, military personnel were not tested at that time for G6PD

deficiency. Current practice makes this information routinely available on all Naval personnel, and carries the implication that testing is for the purpose of preventing adverse reactions. Under these circumstances, it might be difficult to justify an adverse reaction caused by administering primaquine to a known G6PD deficient individual, even though such an event might be quite rare. This is particularly true in the face of the Centers for Disease Control, The Medical Letter, and the World Health Organization all proscribing, to at least some degree, the administration of primaquine to G6PD deficient individuals.

USING PRIMAQUINE IN G6PD DEFICIENT INDIVIDUALS

Several different regimens have been proposed for using primaquine, either prophylactically or for radical cure of an overt infection. All regimens can be tolerated by individuals who are not G6PD deficient. The difference lies in their toleration by individuals who are G6PD deficient. The efficacy of primaquine treatment is directly related to the total dose received. Regimens that divide the total dose into numerous small doses, spread out over a longer period of time, attempt to achieve equal efficacy by having the patient eventually consume the same total amount of primaquine as with shorter, more intense regimens. The smaller doses are felt to be less likely to produce hemolysis, or to produce less severe hemolysis. However evidence is lacking that this strategy is truly effective in reducing the severity of hemolysis. The inherent disadvantage of such regimens is that as the duration of taking primaquine lengthens, compliance may lessen.

One tablet of primaquine contains 26.3 mg of primaquine phosphate (15 mg base). A chloroquine-primaquine tablet (C-P tablet) contains 500 mg chloroquine phosphate (300 mg base) plus 78.9 mg primaquine phosphate (45 mg base). Thus, a C-P tablet contains the equivalent amount of primaquine to that found in three regular primaquine tablets. Based upon this, several options are available for radical cure treatment, or chemoprophylaxis, of P. vivax or P. ovale malaria:

- One primaquine tablet daily for 14 days.
- Three primaquine tablets once weekly for 8 weeks, (24 tablets total dose). or One C-P tablet weekly for 8 weeks, (8 C-P tablets total dose).
- No primaquine at all. Treat the vivax or ovale infections as they occur or recur, with chloroquine alone. After one or two recurrences, the infection will usually have been eliminated.

Historically, the second regimen, weekly dosing for eight weeks, has been used by Navy and Marine Corps personnel. This may be appropriate for radical cure of vivax or ovale infections, however the third option is probably preferred for chemoprophylaxis of G6PD deficient individuals.

SIGNS AND SYMPTOMS OF HEMOLYSIS

SYMPTOMS

There are only a limited number of symptoms. They are nonspecific and generally appear only after a significant amount of hemolysis has occurred. Patients can be told to watch for dark urine (due to hemoglobin in the urine), and the symptoms of anemia (rapid pulse, shortness of breath, rapid breathing, and tiredness).

These symptoms of anemia may first occur after physical exertion, especially vigorous exertion, leaving the individual with the feeling that he is "out of shape." Such symptoms are particularly significant in combat troops and other individuals who would normally be expected to be physically fit. With severe anemia, these signs and symptoms may become apparent with minimal exertion, or even at rest. Some individuals may go into shock (cardiovascular collapse).

Dark urine, and the symptoms of anemia, are obviously nonspecific signs and symptoms, which may be due to many different causes besides hemolysis. Therefore any individual suspected of having a hemolytic reaction should be referred to a medical officer for evaluation as soon as possible.

LABORATORY TESTS

There are several laboratory tests which may suggest hemolysis. Many of them can easily be done in the field. The simplest laboratory test is the urine dipstick, which will show hemoglobin in the urine, and possibly urobilinogen. Because the RBCs have been destroyed by the hemolytic process, there should be few if any RBCs in the urine, even though the dipstick may be strongly positive for hemoglobin. Another simple laboratory test is the hematocrit, which will be reduced to a varying degree after hemolysis.

Other tests, of varying availability, include the blood hemoglobin (decreased), plasma hemoglobin (increased), plasma haptoglobin (decreased), reticulocyte count (increased), and LDH (variably increased). Heinz bodies (precipitated hemoglobin in the RBC) may be seen in the first few days of a hemolytic crisis. Although Heinz bodies are a "classic" finding, a special stain is required to demonstrate them.

COUNSELING OF INDIVIDUALS WHO ARE G6PD DEFICIENT

G6PD-deficient service members should be told that they are G6PD-deficient and be counseled as to the meaning of this, its relationship to antimalarials, and when to seek medical evaluation.

Because G6PD deficient individuals may not be able to utilize all the antimalarial compounds other individuals can, they should be particularly well counseled as to the need for personal protection measures, and the need to immediately report for medical evaluation if they have any symptoms compatible with malaria. This is especially true if they have not received primaquine terminal prophylaxis after leaving a malarious area.

This counseling should be documented in the health record.

CHAPTER TWELVE

NAVY RESPONSIBILITIES IN MALARIA CONTROL

Malaria is an extremely important disease to Naval personnel. Everyone, from the sailor or Marine in the field to those in authority, needs to take responsibility for malaria prevention and control. Specific responsibilities for prevention and control, as determined by an individual's position or occupational specialty, are discussed below.

FLEET AND FORCE COMMANDERS

Fleet and force commanders whose units are either stationed in, or subject to operations in, malaria risk areas must direct their subordinate commands to maintain adequate supplies of material for malaria prevention and control. Such supplies include sufficient amounts of drugs for chemoprophylaxis and therapy, materials for vector control, and personal protection items. Use of these materials by subordinate commands as well as all other recommended malaria control measures must be enforced.

COMMANDING OFFICERS

Commanding Officers must ensure that all command personnel receive adequate instruction in individual malaria prevention and are placed on appropriate chemoprophylaxis prior to, during, and after a deployment to a malarious area. The appropriate chemoprophylactic regimen will be chosen by the command's senior medical department representative after consulting with the cognizant Navy Environmental and Preventive Medicine Unit (NAVENPVNTMEDU). Enforcement of the use of personal protection measures is also the responsibility of Commanding Officers. Finally, Commanding Officers must ensure that a Disease Alert Report (DAR) has been submitted on all suspected or confirmed cases of malaria within the command.

MEDICAL DEPARTMENT

The Medical Department malaria prevention and control program consists of many elements, including: education and training; surveillance and sometimes treatment of the local population in malarious areas; chemoprophylaxis; medical management of malaria cases; personal protection measures; vector surveillance and control; and program management. Responsibilities for program elements are divided among Medical Department personnel and are detailed in the following paragraphs.

The primary goals of Medical Department personnel tasked with malaria prevention and control are instructing susceptible personnel and ensuring their compliance with individual prevention measures. It is essential that a well-defined education program be developed and established. This should include recognition of the signs and symptoms of malaria infection, the ways malaria is transmitted, and the methods of control and prevention. It is equally important to stress compliance with chemoprophylaxis and personal protection measures. Medical Department personnel must be aware of conditions such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, pregnancy, and a history of adverse reactions to antimalarials which may require specialized chemoprophylactic and/or treatment regimens.

Consultation with the cognizant NAVENPVNTMEDU prior to deployment to malaria risk areas is another important function of the Medical Department personnel. The cognizant NAVENPVNTMEDU will provide the most up-to-date advice and assistance on any necessary variations from standard approaches to malaria chemoprophylaxis and treatment, malaria risk assessments, and vector control. The NAVENPVNTMEDU can also provide the latest Disease Risk Assessment Profile (DISRAP), which will describe the malaria risk for the countries of interest.

Consultation with the cognizant Navy Disease Vector Ecology and Control Center (NAVDISVECTECOLCONCEN) may also be necessary to obtain specialized advice and assistance regarding entomology and geographic risk assessments, vector control, and personal protection measures. Additional advice on the mosquito vectors likely to be encountered in specific countries can be obtained from the NAVDISVECTECOLCONCEN in the form of a Vector Risk Assessment Profile (VECTRAP).

Predeployment briefings for Medical Department Representatives (MDRs) are also available at the NAVENPVNTMEDUs and NAVDISVECTECOLCONCENs. Consultation is also available from these sources when there is a need to advise other commands or health care beneficiaries prior to deployment or travel to malaria risk areas.

MEDICAL OFFICERS

FORCE MEDICAL OFFICERS

Prior to deployment, Fleet and Force Medical Officers should advise their respective commanders as to the need for malaria control measures, as determined by the disease threat information provided by the cognizant NAVENPVNTMEDU. Force

Medical Officers are responsible for ensuring that Medical Department personnel under their cognizance are familiar with prevention, recognition, and treatment of malaria. In addition, they should assist, as needed, with the education of all deploying personnel regarding malaria prevention and control. The Force Medical Officer will also ensure that an appropriate chemoprophylactic regimen has been identified and will be implemented. All Medical Officers deployed in malarious areas must set an appropriate example by their personal compliance with all recommended personal protection actions and chemoprophylactic drug regimens.

SENIOR MEDICAL OFFICERS
GENERAL MEDICAL OFFICERS

Medical Officers assigned to commands or units located in, operating in, or deploying to malaria risk areas must be thoroughly familiar with the prevention, diagnosis, and treatment of malaria prior to entering a possible malaria transmission zone. They are responsible for developing and carrying out malaria prevention education programs within their units and for supervising chemoprophylaxis programs. Medical Officers must ensure that all hospital corpsmen under their supervision know how and when to suspect an initial diagnosis of malaria and how to institute proper initial patient management. Once the diagnosis of malaria is suspected, the treatment regimen needs to be under the direct supervision of a Medical Officer. All flight personnel undergoing treatment for clinical malaria must be grounded until resumption of their flight status is approved by a Flight Surgeon. Medical Officers must be thoroughly familiar with the side effects and complications of antimalarial drugs. All Medical Officers deployed in malarious areas must set an appropriate example by their personal compliance with all recommended personal protection actions and chemoprophylactic drug regimens.

PREVENTIVE MEDICINE OFFICERS

The general preventive medicine officer (GPMO) must know the general duties of all other medical personnel involved in malaria control. This includes the Medical Entomologists, Environmental Health Officers (EHO), and the Preventive Medicine Technicians (PMT). He/she must be able to provide training, updating, review, and consultation to all Medical Officers, EHOs, IDTs, and PMTs, whether stationed at hospitals, clinics, ships, or Marine units, within his/her area of responsibility. This training should include diagnosis (clinical and laboratory), treatment, and prophylaxis. (Laboratory diagnosis classes should be taught under the

supervision of the NAVENPVNTMEDU microbiologist and his/her technicians.)

The GPMO should know both the essentials for completing a malaria survey as a research tool using the World Health Organization protocol and for doing a quick mini-survey under hostile conditions. He/She should be able to mount out a malaria survey team with all necessary personnel and equipment and accomplish the survey with minimal support and time. As an epidemiologist, the GPMO should continuously monitor all malaria Disease Alert Reports. He/She should maintain constant communication with NAVENPVNTMEDU epidemiologists and maintain a dialogue with local health officials and malaria experts within his/her area of responsibility. He/She must maintain current knowledge on malaria prevalence, incidence, and drug resistance patterns in all operational areas including nearby ports and staging areas. All Medical Officers deployed in malarious areas must set an appropriate example by their personal compliance with all recommended personal protection actions and chemoprophylactic drug regimens.

FLIGHT SURGEONS

Chemoprophylaxis regimens for flight personnel may be restricted to certain drugs, and may differ from a regimen for non-flight personnel in the same geographic area. Flight personnel who are on malaria chemoprophylaxis may need to be evaluated by their Flight Surgeon periodically, at an interval to be determined by the prevailing standards of practice in aviation medicine. Flight personnel undergoing treatment for clinical malaria are grounded for the duration of such therapy and until resumption of flight status is approved by a Flight Surgeon. All Medical Officers deployed in malarious areas must set an appropriate example by their personal compliance with all recommended personal protection actions and chemoprophylactic drug regimens.

HOSPITAL CORPSMEN

All hospital corpsmen assigned to commands located in, or deployed to, malarious areas must be intimately involved in the command malaria education and control program. Specific responsibilities include being thoroughly familiar with the use and importance of personal protection measures, instructing unit personnel in proper prevention techniques, supervising chemoprophylaxis programs, and performing the Wilson-Edeson test. All corpsmen should know when to suspect an individual is infected with malaria. Independent Duty Corpsmen should know how to institute the proper initial treatment of malaria if necessary. Further therapy should be under the direct

supervision of a Medical Officer, if possible. If not, it should be via consultation with a Medical Officer. All corpsmen deployed in malarious areas must set an appropriate example by their personal compliance with all recommended personal protection actions and chemoprophylactic drug regimens.

PREVENTIVE MEDICINE TECHNICIANS

Preventive Medicine Technicians need to be directly involved in all aspects of the malaria control program. They should be able to assist all other medical department personnel in carrying out their responsibilities for malaria control. In addition, they have the primary responsibility for educating personnel on the need for and benefits of personal protection measures. When necessary, they are also responsible for obtaining vector intelligence and surveillance information, collecting epidemiology data, submitting Disease Alert Reports, and conducting vector control measures when appropriate. All corpsmen deployed in malarious areas must set an appropriate example by their personal compliance with all recommended personal protection actions and chemoprophylactic drug regimens.

LABORATORY OFFICERS AND LABORATORY TECHNICIANS

Laboratory officers and technicians assigned to commands located in, or deployed to, malarious areas must be familiar with the proper preparation and staining of malaria blood smears and identification of Plasmodium parasites. Duplicates of all blood smears prepared for a suspected or confirmed case of malaria should be sent to the cognizant NAVENPVNTMEDU for confirmation of the diagnosis and species. Both stained and unstained thick and thin smears should be sent, along with pertinent identifying information and clinical history. Laboratory officers and technicians must also be proficient in performing and interpreting the Wilson-Edeson test.

ENVIRONMENTAL HEALTH OFFICERS

Environmental Health Officers should be prepared to assist in the collection of epidemiologic and entomologic data, in the education of personnel in malaria prevention and control, and in the evaluation of environmental conditions affecting malaria control. They should be prepared to coordinate vector control efforts in the absence of a medical entomologist.

MEDICAL ENTOMOLOGISTS

Medical entomologists are responsible for obtaining the most current mosquito intelligence and surveillance information for their geographic areas and instituting any necessary control programs. They may also be responsible for educating personnel and making recommendations to the command regarding the appropriate use of personal protection measures, including repellents, protective clothing and gear, and bed nets. Medical entomologists are also responsible for advising unit commanders on the location of camp sites, recommended modifications of training schedules and field exercises, the performance of adult and larval mosquito surveys, and pesticide application.

PROGRAM MANAGEMENT

MEDICAL RECORDS

Medical records of Naval personnel and other health care beneficiaries must contain the following information:

(1) Prior to deployment or visit to a malarious area:

(a) Glucose-6-phosphate dehydrogenase (G6PD) test results. It is required that all Navy, Marine Corps, and Military Sealift Command personnel be screened for this deficiency and that the results be permanently recorded on a Standard Form 600 (SF 600) in their health records. All personnel found to be G6PD deficient must have this information listed on their Problem Summary List (NAVMED 6150/20), should have the "Sensitivities" block (in the "Alert" box) on the cover of their medical treatment record checked, and should be issued a medical warning tag. Other health care beneficiaries must be offered this screening test. Individuals whose G6PD test shows a normal amount of G6PD must have this fact entered in their health records, to document this fact and avoid unnecessary additional testing.

(b) The date of initiation of malaria chemoprophylaxis, and the type and amount of medication(s), prescribed, must be entered in the health record.

(2) During and after deployment or visit to a malarious area:

(a) The date of initiation of terminal chemoprophylaxis along with the type and amount of medications prescribed.

(b) The date of completion of malaria chemoprophylaxis.

(c) The date and results of all Wilson-Edeson tests performed, if any.

(d) Full documentation of diagnostic procedures and treatments undertaken in the event of the occurrence of suspected or confirmed clinical malaria.

All individuals who are placed on malaria chemoprophylactic agents should be carefully and thoroughly instructed as to why the medicine is being prescribed for them, how it is to be taken, the possible side effects of the medication, and the fact that chemoprophylaxis reduces the chances of becoming infected, but does not guarantee they will not get infected. Personnel should also be instructed to report to the Medical Department immediately if any signs or symptoms of malaria develop. (See Chapter 4, "Diagnosis, Clinical Presentation, and Clinical Course," to review signs and symptoms.) Instructions must also be given regarding the proper use of personal protection measures such as DEET, permethrin, and netting. (Personal protection is covered in Chapter 8, "Malaria Personal Protection Measures.")

Overprinted or special SF 600 forms may be used for documenting the preceding information. An example of this is given in Appendix 7.

DISEASE ALERT REPORTS (DARS)

Suspected or confirmed malaria cases must be reported in accordance with NAVMEDCOMINST 6220.2 and 6230.2 series. The DAR must be sent to the nearest NAVENPVNTMEDU. A DAR should also be sent the NAVENPVNTMEDU serving the ship or unit's homeport or home base, if this is not the nearest NAVENPVNTMEDU. Information copies must be sent to the Navy Environmental Health Center, the nearest NAVDISVECTECOLCONCEN, and the Naval Hospital in the area where it is suspected the patient contracted malaria. If it is suspected that the patient's strain of malaria parasites is drug resistant (because of their geographic origin or the failure of prophylactic chloroquine to prevent transmission), this information should be included on the DAR.

The following information must also be included in the DAR: a) The patient's itinerary during the previous three months (and if appropriate, even longer, up to two years), b) Types and duration of any chemoprophylaxis or treatment medications taken, c) Results of the Wilson-Edeson test prior to therapeutic treatment, or a statement that the test was not done, d) Interpretation of any blood smears performed, e) Date of shipment of stained and unstained blood smear slides to the

nearest NAVENPVNTMEDU for confirmation. If the patient has received any blood transfusions outside of the United States, this fact should be noted also, along with the location and date the transfusion was received.

MEDICAL TREATMENT FACILITIES

Physicians at medical treatment facilities or other units managing malaria patients, should be familiar with the importance of monitoring parasitemia before, during and following the therapeutic treatment of individuals for malaria. Thick and thin peripheral blood smears must be prepared for the diagnosis of suspected malaria patients as well as during regular intervals for the remainder of the treatment period to ensure that complete eradication of parasites from the blood has occurred. If the patient is transferred to another facility, his blood smears should be transferred with him so that the diagnosis can be confirmed by experienced laboratory personnel at the earliest opportunity. (Refer to Appendix 3, "Laboratory Diagnosis of Malaria.")

MEDICAL BOARD EVALUATION

Personnel suffering an attack of malaria characterized by severe hemolytic reactions such as "blackwater fever" (hemolysis, hemoglobinuria, and renal failure) must be evaluated by a Medical Board. Personnel who suffer a severe hemolytic reaction to malaria chemoprophylactic agents should also be evaluated by a Medical Board to determine whether subsequent assignments can include areas endemic for malaria, and overall fitness for duty. Cerebral malaria is not considered a contraindication for subsequent reassignment to a malaria risk area.

BLOOD DONOR PROGRAMS

Blood donor programs are under the overall guidance of NAVMED P-5120, "Standards for Blood Banks and Transfusion Services." Individuals who were treated for malaria in the past must wait three years from the date treatment was finished until they are eligible to donate blood. Individuals who were in malaria risk areas and who took chemoprophylaxis, must also wait three years from the time chemoprophylaxis was finished before donating blood.

Individuals who visited a malaria risk area and remained asymptomatic, but were not required to take chemoprophylaxis because of negligible risk of exposure, or who simply avoided taking any prophylaxis, must wait six months after leaving the malarious area until they are eligible to donate blood.

Individuals who were placed on chemoprophylaxis initially because of intended travel into a malaria risk area, but who did not actually visit the area, have no required waiting period. These waiting times apply to military blood banks and civilian blood collection agencies.

APPENDIX 1

TABLE 7

SUMMARY OF MALARIA EXPERIENCE IN THE NAVAL FORCES

TABLE 7

SUMMARY OF MALARIA EXPERIENCE IN THE NAVAL FORCES

TIME PERIOD	AVERAGE STRENGTH	ADMISSION SDUE TO MALARIA	NE RATIO DUE TO MALARIA	ADM RATE FOR ALL DISEASES AND CONDITIONS	ADMIN RATE FOR MALARIA
WWI					
CY 1917	245,580	2,045	32	53,488	833
CY 1918	503,792	2,701	22	77,627	536
WWII					
CY 1941	348,926	392	6	43,817	112
CY 1942	834,639	12,643	36	46,173	1,515
CY 1943	2,108,379	56,436	253	60,279	2,677
CY 1944	3,349,798	29,452	69	42,871	879
CY 1945	3,673,855	12,752	3	39,997	347
KOREAN WAR					
CY 1950	538,179	61	0.4	30,819	11
CY 1951	915,024	854	3	32,640	93
CY 1952	1,052,327	1,125	4	29,721	107
CY 1953	1,052,145	2,357	6	29,000	224
VIETNAM CONFLICT	878,185	80	0.3	17,383	9 1/1-6/30
CY 1962	*	*	*	*	*
FY 1963	879,265	21	0.2	15,371	2
FY 1964	879,360	*	*	*	*
FY 1965	935,800	624	*	16,007	67
FY 1966	1,026,187	2,303	*	16,722	224
FY 1967	1,049,982	2,853	*	18,628	272
FY 1968	1,069,892	7,518	33	19,616	703
FY 1969	1,062,959	4,938	*	18,605	929 7/1-1/31
FY 1969	956,063	2,735	13	14,250	286
FY 1970	840,582	506	4	13,901	60
FY 1971	789,690	66	0.3	12,875	8
FY 1972	761,003	51	0.4	11,891	7
FY 1973					

NOTE 1: CY = CALENDAR YEAR
NOTE 2: FY = FISCAL YEAR RUNNING FROM JULY 1 THROUGH THE FOLLOWING JUNE 30
NOTE 3: ALL ADMISSION RATES (ADM RATES) ARE EXPRESSED AS NEW ADMISSIONS PER 100,000 PERSONS - YEARS.
NOTE 4: THE NONEFFECTIVE RATIO (NE RATIO) IS EXPRESSED PER 100,000 AVERAGE STRENGTH. THE NONEFFECTIVE RATIO IS A MEASURE OF THE TEMPORARY MANPOWER LOSS TO THE NAVAL FORCES DUE TO A PARTICULAR MEDICAL CAUSE. IT TELLS THE AVERAGE NUMBER OF PERSONNEL ON THE DAILY CENSUS OF A NAVAL MEDICAL TREATMENT FACILITY IN THE GIVEN TIME PERIOD PER 100,000 AVERAGE STRENGTH WHO, THEREFORE, WERE NOT AVAILABLE FOR ACTIVE DUTY.
NOTE 5: *DENOTES MISSING DATA SECONDARY TO A CHANGE IN REPORTING.

APPENDIX 2

WORLDWIDE MALARIA MAP

MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

(From The Centers for Disease Control
Health Information for International Travel)

Figure 5

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Afghanistan *Yellow Fever*-II	All	Confirmed	B
Albania *Yellow Fever*-II > 1 yr	None		
Algeria *Yellow Fever*-II > 1 yr	Very limited risk in Sahara Region.	None	None
Andorra No vaccinations are required.	None		
Angola *Yellow Fever**-II > 1 yr	All	Confirmed	B
Antigua and Barbuda *Yellow Fever*-II > 1 yr	None		
Argentina No vaccinations are required. *Yellow Fever**[†]-	Rural areas near Bolivian border, i.e., Salta and Jujuy Provinces.	None	A

[†]Risk in northeastern forest areas only.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Armenia-Follow former USSR regulations until further notice.	None		
Australia *Yellow Fever*-III > 1 yr A certificate is also required of travelers who have within the previous 6 days been in a country infected with yellow fever. Note: Australia is not bound by the International Health Regulations	None		
Austria No vaccinations are required.	None		
Azerbaijan-Follow former USSR regulations until further notice.	Exists in some very small southern border areas.	None	A

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Azores(Portugal) *Yellow Fever*-II > 1 yr Except that NO certificate is required from travelers in transit at Santa Maria.	None		
Bahamas *Yellow Fever*-II > 1 yr	None		
Bahrain No vaccinations are required.	None		
Bangladesh *Yellow Fever*-III A certificate is required ALSO from travelers arriving from or transiting: Africa: Angola; Benin; Botswana; Burkina Faso; Burundi; Cameroon; Central African Republic; Chad; Congo; Côte d'Ivoire; Equatorial Guinea; Ethiopia; Gabon; Gambia; *(Continued on next page)*	All areas, except no risk in city of Dhaka.	Widespread in areas along the northern and eastern border.	B

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):
Regimen A - Routine weekly prophylaxis with chloroquine alone.
Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Bangladesh(Cont'd) Ghana; Guinea; Guinea-Bissau; Kenya; Liberia; Malawi; Mali; Mauritania; Niger; Nigeria; Rwanda; Sao Tome and Principe; Senegal; Sierra Leone; Somalia; Sudan (south of 15°N); Tanzania, United Republic of; Togo; Uganda; Zaire; Zambia. Americas: Belize; Bolivia; Brazil; Colombia; Costa Rica; Ecuador; French Guiana; Guatemala; Guyana; Honduras; *(Continued on next page)*			

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Bangladesh(Cont'd) Nicaragua; Panama; Peru; Suriname; Venezuela. Caribbean: Trinidad and Tobago. Any person (including infants) arriving by air or sea without a certificate within 6 days of departure from or transit through an infected area will be isolated up to 6 days.			
Barbados *Yellow Fever*-II > 1 yr	None		
Belarus-Follow former USSR regulations until further notice.	None		
Belgium No vaccinations are required.	None		
Belize *Yellow Fever*-II *(Continued on next page)*	Rural areas (including forest preserves and offshore islands,	None	A

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):
Regimen A - Routine weekly prophylaxis with chloroquine alone.
Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Belize(Cont'd)	including the resort areas) except no risk in central coastal District of Belize.		
Benin (formerly Dahomey) *Yellow Fever**-I > 1 yr	All	Confirmed	B
Bermuda(U.K.) No vaccinations are required.	None		
Bhutan *Yellow Fever*-II	Rural areas in districts bordering India.	Confirmed	B
Bolivia *Yellow Fever**-II Bolivia recommends vaccination for all travelers from non-infected areas, who are destined for risk areas *(Continued on next page)*	Rural areas only, except no risk in highland areas, i.e., Oruro Dept. and Prov. of Ingavi, Los Andes, Omasuyos, and Pacajes, (La Paz Dept) and southern	Confirmed	B

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Bolivia(Cont'd)	and central Potosi Department.		
such as the Departments of Beni, Chuquisaca, Cochabamba, Pando, Santa Cruz, Tarija, and part of La Paz Department			
Bosnia/Herzegovina- Follow Yugoslavia regulations until further notice.	None		
Botswana			
No vaccinations are required.	Northern part of country (North of 21°S.)	Confirmed	B
Brazil			
*Yellow Fever**-II > 9 mo, unless they are in possession of a waiver stating that immunization is contraindicated on medical grounds. A certificate is ALSO required from travelers arriving from: Africa: Angola, Cameroon, Gambia, Guinea, Mali, Nigeria, Sudan, Zaire	Acre and Rondonia States Terr. of Amapá and Roraima, and in part of rural areas of Amazonas, Maranhao, Mato Grosso, Pará and Tocantins States[1].	Confirmed	B

(Continued on next page)

[1]Travelers who will only visit the coastal States from the horn to the Uruguay border and Iguassu Falls are not at risk and need no prophylaxis.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):
Regimen A - Routine weekly prophylaxis with chloroquine alone.
Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Brazil(Cont'd) Americas: Bolivia, Ecuador, Colombia, Peru Brazil recommends vaccination for travel to rural areas in Acre, Amazonas, Goiás, Maranhão, Mato Grosso, Mato Grosso do Sul, Pará and Rondônia States and Territories of Amapá and Roraima.			
Brunei Darussalam *Yellow Fever*-II > 1 yr A certificate is required ALSO from travelers coming from or transiting endemic zones within the preceding 6 days.	None		
Bulgaria No vaccinations are required.	None		

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Burkina Faso (formerly Upper Volta) *Yellow Fever**-I > 1 yr	All	Confirmed	B
Burma(see Myanmar)			
Burundi *Yellow Fever**-II > 1 yr	All	Confirmed	B
Cambodia *Yellow Fever*-II	All, except no risk in Phnom Penh.	Confirmed	B
Cameroon *Yellow Fever**-I > 1 yr	All	Confirmed	B
Canada No vaccinations are required.	None		
Canary Islands(Spain) No vaccinations are required.	None		
Cape Verde *Yellow Fever*-III > 1 yr Required from travelers coming from countries having reported cases in the last 6 years.	Limited to Island of São Tiago	None	None

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Cayman Islands(U.K.) No vaccinations are required.	None		
Central African Republic *Yellow Fever**-I > 1 yr	All	Confirmed	B
Chad *Yellow Fever**- No vaccination is required, however, Chad recommends vaccination for all travelers > 1 yr of age.	All	Confirmed	B
Chile No vaccinations are required.	None		
China *(Continued on next page)*	Rural areas only except no risk in	Confirmed in southern China; Hainan Island, and	A/B[2]

[2]Travelers visiting cities and popular rural sites on usual tourist routes are generally not at risk, and chemoprophylaxis is, therefore, not recommended. Travelers on special scientific, educational, or recreational visits should check whether their itineraries include evening or nighttime exposure in areas of risk, or in areas of chloroquine resistance. Travelers to most areas of risk within China should follow Regimen A; travelers to areas of chloroquine resistance should follow Regimen B.

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
China(Cont'd) *Yellow Fever*-II	northern provinces bordering Mongolia and in the western provinces of Heilungkiang, Kirin, Ningsia Hui Tibet and Tsinghai. North of 33° N latitude transmission occurs July to November; between 33° and 25° N latitude transmission occurs May to December; south of 25° N latitude transmission occurs year-round.	provinces bordering Myanmar (formerly Burma), Lao People's Democratic Republic and Viet Nam	
Christmas Island(Australia) *Yellow Fever*-III > 1 yr A certificate is also required of travelers who have within the previous 6 days been in a country infected with yellow fever. Note: Christmas Island is not bound by the International Health Regulations.	None		

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Colombia *Yellow Fever**- No vaccination required, however, Colombia recommends vaccination for travelers to the middle valley of the Magdalena River, eastern and western foothills of the Cordillera Oriental from the frontier with Ecuador to that with Venezuela, Urabá, foothills of the Sierra Nevada, eastern plains (Orinoquia) and Amazonia.	Rural areas only, except no risk in Bogota and vicinity[3]	Confirmed	B
Comoros No vaccinations are required.	All	Confirmed	B
Congo *Yellow Fever**-I > 1 yr	All	Confirmed	B

[3]Risk exists in rural areas of Uraba (Antioquia Dept.), Bajo Cauca-Nechi (Cauca and Antioquia Dept.), Magdalena Medio, Caqueta (Caqueta Intendencia), Sarare (Arauca Intendencia), Catatumbo (Norte de Santander Dept.), Pacifico Central and Sur, Putumayo (Putumayo Intendencia), Ariari (Meta Dept.), Alto Vaupes (Vaupes Comisaria), Amazonas, and Guainia (Comisarias).

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Cook Islands(New Zealand) No vaccinations are required.	None		
Costa Rica No vaccinations are required.	Rural areas only, except there is no risk in central highlands, i.e., Cartago and San Jose Provinces.	None	A
Côte d'Ivoire (formerly Ivory Coast) *Yellow Fever**-I > 1 yr	All	Confirmed	B
Croatia No vaccinations are required.	None		
Cuba No vaccinations are required.	None		
Cyprus No vaccinations are required.	None		
Czech Republic No vaccinations are required.	None		

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Denmark No vaccinations are required.	None		
Djibouti *Yellow Fever*-II > 1 yr	All	Confirmed	B
Dominica *Yellow Fever*-II > 1 yr	None		
Dominican Republic No vaccinations are required.	All rural areas except no risk in tourist resorts. Highest risk in provinces bordering Haiti.	None	A
Ecuador *Yellow Fever**-II > 1 yr	All areas in the provinces along the eastern border and the pacific coast, i.e., Esmeraldas, El Oro, Guayas (including Guayaquil), Los Rios, Manabi,	Confirmed	B

(Continued on next page)

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Ecuador(Cont'd)	Morona-Santiago, Napo, Pastaza, Pinchincha, Sucumbios, and Zamora-Chinchipe provinces[4].		
Egypt *Yellow Fever*-II > 1 yr A certificate is required ALSO from travelers arriving from or transiting: Africa: Angola; Benin; Botswana; Burkina Faso; Burundi; Cameroon; Central African Republic; Chad; Congo; Côte d'Ivoire; Equatorial Guinea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Kenya; Liberia; Malawi; Mali; Mauritania; Niger; *(Continued on next page)*	Rural areas of Nile Delta, El Faiyum area, the oases, and part of southern (upper) Egypt.[5]	None	A

[4]Travelers who will only visit Quito and vicinity, the central highland tourist areas, or the Galapagos Is. are not at risk and need no prophylaxis.
[5]Travelers who will only visit the main tourist areas, including the cruises, are not at risk and need no prophylaxis.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):
Regimen A - Routine weekly prophylaxis with chloroquine alone.
Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Egypt(Cont'd) Nigeria; Rwanda; Sao Tome and Principe; Senegal; Sierra Leone; Somalia; Sudan (south of 15°N); Tanzania, United Republic of; Togo Uganda; Zaire; Zambia. Americas: Belize; Bolivia; Brazil; Colombia; Costa Rica; Ecuador; French Guiana; Guatemala; Guyana; Honduras; Nicaragua; Panama; Peru; Suriname; Venezuela. Caribbean: Trinidad and Tobago *(Continued on next page)*			

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Egypt(Cont'd) Air passengers in transit coming from these countries or areas without a certificate will be detained in the precincts of the airport until they resume their journey. All travelers arriving from Sudan are required to possess a vaccination certificate or a location certificate issued by a Sudanese official center stating that they have not been in that part of Sudan south of 15°N latitude within the preceding 6 days.			
El Salvador *Yellow Fever*-II > 6 mo	Rural areas only.	None	A
Equatorial Guinea *Yellow Fever**-II	All	Confirmed	B
Eritrea *Yellow Fever*-II	All areas except no risk above 2,000 meters.	Confirmed	B
Estonia-Follow former USSR regulations until further notice.	None		

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Ethiopia *Yellow Fever**-II > 1 yr	All areas except no risk in Addis Ababa and above 2,000 meters.	Confirmed	B
Falkland Islands (U.K.) No vaccinations are required.	None		
Faroe Islands(Denmark) No vaccinations are required.	None		
Fiji *Yellow Fever*-II > 1 yr	None		
Finland No vaccinations are required.	None		
France No vaccinations are required.	None		
French Guiana *Yellow Fever**-I > 1 yr	All	Confirmed	B

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III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

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> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
French Polynesia(Tahiti) *Yellow Fever*-II > 1 yr	None		
Gabon *Yellow Fever**-I > 1 yr	All	Confirmed	B
Gambia *Yellow Fever**-II > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones.	All	Confirmed	B
Georgia-Follow former USSR regulations until further notice.	None		
Germany No vaccinations are required.	None		
Ghana *Yellow Fever**-I	All	Confirmed	B
Gibraltar(U.K.) No vaccinations are required.	None		

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Greece *Yellow Fever*-II > 6 mo	None		
Greenland (Denmark) No vaccinations are required.	None		
Grenada *Yellow Fever*-II > 1 yr	None		
Guadeloupe(France) *Yellow Fever*-II > 1 yr	None		
Guam(U.S.) No vaccinations are required.	None		
Guatemala *Yellow Fever*-III > 1 yr	Rural areas only, except no risk in central highlands.	None	A
Guinea *Yellow Fever**-II > 1 yr	All	Confirmed	B

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> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Guinea-Bissau *Yellow Fever**-II > 1 yr A certificate is required ALSO from travelers arriving from: Africa: Angola; Benin; Burkina Faso; Burundi; Cape Verde; Central African Republic; Chad; Congo; Côte d'Ivoire; Djibouti; Equatorial Guinea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Kenya; Liberia; Madagascar; Mali; Mauritania; Mozambique; Niger; Nigeria; Rwanda; Sao Tome and Principe; Senegal; Sierra Leone; Somalia; Tanzania, United Republic of Togo; *(Continued on next page)*	All	Confirmed	B

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Guinea-Bissau(Cont'd) Uganda; Zaire; Zambia. Americas: Bolivia; Brazil; Colombia; Ecuador; French Guiana; Guyana; Panama; Peru; Suriname; Venezuela.			
Guyana *Yellow Fever**-II A certificate is required ALSO from travelers arriving from: Africa: Angola; Benin; Burkina Faso; Burundi; Cameroon; Central African Republic; Chad; Congo; Côte d'Ivoire; Gabon; Gambia; Ghana; *(Continued on next pate)*	Rural areas in the southern interior and northwest coast, i.e., Rupununi and North West Regions.	Confirmed	B

EXPLANATION OF VACCINATION CODES:

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* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Guyana(Cont'd) Guinea; Guinea-Bissau; Kenya; Liberia; Mali; Niger; Nigeria; Rwanda; Sao Tome and Principe; Senegal; Sierra Leone; Somalia; Tanzania, United Republic of; Togo; Uganda; Zaire. Americas: Belize; Bolivia; Brazil; Colombia Costa Rica; Ecuador; French Guiana; Guatemala; Honduras; Nicaragua; Panama; Peru; Suriname; Venezuela.			
Haiti *Yellow Fever*-II	All	None	A
Honduras *Yellow Fever*-II	Rural areas only.	None	A

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Hong Kong(U.K.) No vaccinations are required.	None		
Hungary No vaccinations are required.	None		
Iceland No vaccinations are required.	None		
India *Yellow Fever*-III A certificate is required ALSO from travelers arriving from or transiting: Africa: Angola; Benin; Burkina Faso; Burundi; Cameroon; Central African Republic; Chad; Congo; Côte d'Ivoire; Equatorial *(Continued on next page)*	All areas, including the cities of Delhi and Bombay, except no risk in parts of the States of Himechel Pradesh, Jammu and Kashmir, and Sikkim.	Confirmed	B

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

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* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
India(Cont'd) Guinea; Ethiopia; Gabon; Gambia; Ghana; Guinea-Bissau; Kenya; Liberia; Mali; Niger; Nigeria; Rwanda; Sao Tome and Principe; Senegal; Sierra Leone; Somalia; Sudan; Tanzania, United Republic of Togo; Uganda; Zaire; Zambia. Americas: Bolivia; Brazil; Colombia; Ecuador; French Guiana; Guyana; Panama; Peru, Suriname; Venezuela. Caribbean: Trinidad and Tobago. Any person (except infants up to the age of 6 mos.) arriving without a certificate within 6 days of departure from or transit through an infected area will be isolated up to 6 days.			

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Indonesia *Yellow Fever*-II A certificate is required ALSO from travelers arriving from countries in the endemic zones.	In general, rural areas only, except high risk in all areas of Irian Jaya (western half of island of New Guinea). No risk in big cities of Java and Sumatra and no risk for the main resort areas of Java and Bali.	Confirmed	B[6]
Iran(Islamic Republic of) No vaccinations are required.	Rural areas only in the provinces of Sistan-Baluchestan, the tropical part of Kerman, Hormozgan, and parts of Bushehr, Fars, Ilam, Kohgiluyeh-Boyar, Lorestan, and Chahar Mahal-Bakhtiari, and the north of Khuzestan.	Confirmed	B

[6]Malaria transmission in Indonesia (except for Irian Jaya) is largely confined to rural areas not visited by most travelers; most travel to rural areas of Indonesia is during daytime hours when there is minimal risk of exposure. Chemoprophylaxis is recommended only for those travelers who will have outdoor exposure during evening and nighttime hours in rural areas.

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

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> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Iraq *Yellow Fever*-II	All areas in northern region, i.e., Duhok, Erbil, Kirkuk, Ninawa, Sulaimaniya Provinces.	None	A
Ireland No vaccinations are required.	None		
Israel No vaccinations are required.	None		
Italy No vaccinations are required.	None		
Jamaica *Yellow Fever*-II > 1 yr	None		
Japan No vaccinations are required.	None		
Jordan *Yellow Fever*- A certificate is required from travelers arriving from countries in the endemic zone in Africa.	None		

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Kazakhstan-Follow former USSR regulations until further notice.	None		
Kenya *Yellow Fever**[†]-II > 1 yr	All areas (including game parks), except no risk in Nairobi, and areas above 2,500 meters.		
Kiribati (formerly Gilbert Islands) *Yellow Fever*-II > 1 yr	None		
Korea, Democratic People's Republic of (North) No vaccinations are required.	None		
Korea, Republic of (South) No vaccinations are required.	None		
Kuwait No vaccinations are required.	None		

[†]CDC currently recommends yellow fever vaccine for all travelers to Kenya.

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VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Kyrgyzstan-Follow USSR regulations until further notice.	None		
Lao People's Democratic Republic *Yellow Fever*-II	All areas except no risk in city of Vientiane.	Confirmed	B
Latvia-Follow USSR regulations until further notice.	None		
Lebanon *Yellow Fever*-II	None		
Lesotho *Yellow Fever*-II	None		
Liberia *Yellow Fever**-I > 1 yr	All	Confirmed	B
Libyan Arab Jamahiriya *Yellow Fever*-II > 1 yr	Very limited risk in two small foci in southwest of country.	None	None
Liechtenstein No vaccinations are required.	None		

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Lithuania No vaccinations are required.	None		
Luxembourg No vaccinations are required.	None		
Macao(Portugal) No vaccinations are required.	None		
Madagascar *Yellow Fever*-II Requirement ALSO includes transiting travelers.	All, highest risk in coastal areas.	Confirmed	B
Madeira(Portugal) *Yellow Fever*-II > 1 yr Except that NO certificate is required from travelers in transit at Funchal and Porto Santo.	None		

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> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Malawi *Yellow Fever*-II	All	Confirmed	B
Malaysia *Yellow Fever*-II > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones.	Peninsular Malaysia and Sarawak (NW Borneo) malaria is limited to the rural hinterland; urban and coastal areas are malaria free. Sabah (NE Borneo) has malaria throughout.	Confirmed	B[7]
Maldives *Yellow Fever*-II	None		
Mali *Yellow Fever**-I > 1 yr	All	Confirmed	B
Malta *Yellow Fever*-II > 9 mo Children under 9 months of age arriving from an infected area may be subject to isolation or surveillance.	None		

[7]Malaria transmission in Malaysia (except Sabah) is largely confined to rural areas not visited by most travelers; most travel to rural areas is during daytime hours when there is minimal risk of exposure. Chemoprophylaxis is recommended only for those travelers who will have outdoor exposure during evening and nighttime hours in rural areas.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Martinique(France) *Yellow Fever*-II > 1 yr	None		
Mauritania *Yellow Fever*-I > 1 yr Except that NO certificate is required from travelers who arrive from a non-infected area and stay less than 2 weeks.	All areas, except no risk in the northern region, i.e., Dakhlet-Nouadhibou, Inchiri, Adrar, and Tiris-Zemour.	Probable	B
Mauritius *Yellow Fever*-II > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones.	Rural areas only, except no risk on Rodriquez Island.	None	A
Mayotte(French territorial collectivity) No vaccinations are required.	All	Confirmed	B

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VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Mexico *Yellow Fever*-II > 6 mos.	Malaria exists in some rural areas of the following states: Oaxaca, Chiapas, Guerrero, Campeche, Quintana Roo, Sinaloa, Michoacan, Nayarit, Colima, Tabasco.[8]	None	A
Micronesia (Federated States of) No vaccinations are required.	None		
Monaco No vaccinations are required.	None		
Mongolia No vaccinations are required.	None		
Montserrat(U.K.) *Yellow Fever*-II > 1 yr	None		
Morocco No vaccinations are required.	Very limited risk in rural areas of some provinces.	None	None

[8]Although chemoprophylaxis is not recommended for travel to the major resort areas on the Pacific and Gulf Coasts, all travelers would be advised to use insect repellents and other personal protection measures.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):
Regimen A - Routine weekly prophylaxis with chloroquine alone.
Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Mozambique *Yellow Fever*-II > 1 yr	All	Confirmed	B
Myanmar(formerly Burma) *Yellow Fever*-II A certificate is required ALSO from nationals and residents of Myanmar departing for an infected area.	Rural areas only.	Confirmed	B[9]
Namibia *Yellow Fever*-II > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones. A certificate is required ALSO from travelers on unscheduled flights, who have transited an infected area. Children under one year of age may be subject to surveillance.	All areas of Ovamboland, and Caprivi Strip.	Confirmed	B

[9]Chemoprophylaxis is recommended only for those travelers who will have outdoor exposure during evening and nighttime hours in rural areas. Travelers who visit the cities of Yangon (formerly Rangoon) and Mandalay are not at risk and need no prophylaxis.

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VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Nauru *Yellow Fever*-II > 1 yr	None		
Nepal *Yellow Fever*-II	Rural areas in Terai Dist. and Hill Districts below 1,200 meters. There is no risk in Katmandu.	Confirmed	B
Netherlands No vaccinations are required.	None		
Netherlands Antilles *Yellow Fever*-II > 6 mo	None		
New Caledonia and Dependencies(France) *Cholera*- Vaccination is not required, however, travelers from infected areas are required to complete a form for the use of the Health Service. *Yellow Fever*-II > 1 yr	None		
New Zealand No vaccinations are required.	None		

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Nicaragua *Yellow Fever*-II > 1 yr	Rural areas only, however, risk exists in outskirts of Bluefields, Bonanza, Chinandega, Leon, Granada, Managua, Nandaime, Puerto Cabeza, Rosita, Siuna and Tipitapa.	None	A
Niger *Yellow Fever**-I > 1 yr Niger ALSO recommends vaccination for travelers leaving the country.	All	Confirmed	B
Nigeria *Yellow Fever**-II > 1 yr	All	Confirmed	B
Niue(New Zealand) *Yellow Fever*-II > 1 yr	None		

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* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Northern Mariana Islands (U.S.) No vaccinations are required	None		
Norway No vaccinations are required	None		
Oman *Yellow Fever*-II	All	Confirmed	B
Pacific Islands, Trust Territory of the U.S.A. No vaccinations are required.	None		
Pakistan *Yellow Fever*-III A certificate is required ALSO from travelers arriving from countries in the endemic zones. A certificate is not required of infants less than 6 months of age if the mother's certificate shows she was vaccinated prior to the birth of the child.	All	Confirmed	B

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Panama *Yellow Fever**- No vaccination required, however, Panama recommends vaccination for travelers who are destined for the province of Darien.	Rural areas of the eastern provinces (Darien and San Blas), northwestern provinces (Boca del Toro and Veraguas), Lake Boyana area and Lake Gatún.	Confirmed in areas east of Canal Zone including San Blas Islands.	A/B[10]
Papua New Guinea *Yellow Fever*-II > 1 yr	All	Confirmed	B
Paraguay *Yellow Fever**-II A certificate is required ALSO from travelers leaving Paraguay going to endemic zones and travelers coming from endemic zones.	Rural areas bordering Brazil.	None	A

[10]There is no risk in the Canal Zone or in Panama City and vicinity. Travelers to rural areas west of the Canal Zone should follow Regimen A; travelers to areas east of the Canal Zone (including the San Blas Islands) should follow Regimen B.

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Peru *Yellow Fever**-II > 6 mo Peru also recommends vaccination for those who intend to visit any rural areas of the country.	Rural areas[11].	Confirmed in provinces bordering Brazil.	A/B[12]
Philippines *Yellow Fever*-II > 1 yr	Rural areas only, except there is no risk in Provinces of Bohol, Catanduanes, Cebu, and Leyte.	Confirmed in Islands of Luzon, Basilan, Mindoro, Palawan, and Mindanao; and Sulu-Archipelago.	A/B[13]
Pitcairn(U.K.) *Yellow Fever*-II > 1 yr	None		
Poland No vaccinations are required	None		

[11]Travelers who will only visit Lima and vicinity, coastal area south of Lima, or the highland tourist areas (Cuzco, Machu Picchu, Lake Titicaca) are not a risk and need no prophylaxis. Risk exists in rural areas of Departments of Amazonas, Cajamarca (except Hualgayoc Province), La Libertad (except Otuzco, Santiago de Chuco Provinces), Lambayeque, Loreto, Piura (except Talara Province), San Martin and Tumbes, Provinces of Santa (Ancash Dept.); parts of La Convension (Cuzco Dept.) Tayacaja (Huancavelica Dept.), Satipo (Junin Dept.).

[12] Travelers to most areas of risk with Peru should follow Regimen A; travelers to the provinces bordering Brazil who will have rural exposure during evening and nighttime hours should follow Regimen B.

[13] Malaria transmission in the Philippines is largely confined to rural areas not visited by most travelers; most travel to rural areas in the Philippines is during daytime hours when there is minimal risk of exposure. Chemoprophylaxis is recommended only for those travelers who will have outdoor exposure during evening and nighttime hours in rural areas. Travelers at risk should use Regimen A, unless they will be at risk in areas of chloroquine resistance, in which case, they should follow Regimen B.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Portugal *Yellow Fever*- A certificate is required ONLY from travelers over 1 year of age arriving from infected areas who are destined for the Azores and Maderia. However, no certificate is required from passengers in transit at Funchal, Porto Santo, and Santa Maria.	None		
Puerto Rico(U.S.) No vaccinations are required.	None		
Qatar *Yellow Fever*-II > 1 yr	None		
Republic of Moldova- Follow former USSR regulations until further notice.	None		

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Reunion(France)	None		
Yellow Fever-II > 1 yr			
Romania	None		
No vaccinations are required.			
Russian Federation-Follow former USSR regulations until further notice.	None		
Rwanda	All	Confirmed	B
*Yellow Fever**-I > 1 yr			
Saint Christopher (Saint Kitts) and Nevis(U.K.)	None		
Yellow Fever-II > 1 yr			
Saint Helena(U.K.)	None		
No vaccinations are required.			
Saint Lucia	None		
Yellow Fever-II > 1 yr			
Saint Pierre & Miquelon(France)	None		
No vaccinations are required.			

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Saint Vincent and the Grenadines *Yellow Fever*-II > 1 yr	None		
Samoa(formerly Western Samoa) *Yellow Fever*-II > 1 yr	None		
Samoa, American(U.S.) *Yellow Fever*-II > 1 yr	None		
San Marino No vaccinations are required.	None		
Sao Tome and Principe *Yellow Fever*-I > 1 yr Except that NO certificate is required from travelers who arrive from a non-infected area and stay less than 2 weeks.	All	Confirmed	B

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

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III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Saudi Arabia *Yellow Fever*-III	All areas in the western provinces except no risk in the high altitude areas of Asir Province (Yemen border), and the urban areas of Jeddah, Mecca, Medina, and Taif.	Suspected	A
Senegal *Yellow Fever**-III A certificate is required ALSO from travelers arriving from or transiting countries in the endemic zones.	All None	Confirmed	B
Serbia/Montenegro- Follow Yugoslavia regulations until further notice.	None		
Seychelles *Yellow Fever*-II > 1 yr	All	Confirmed	B
Sierra Leone *Yellow Fever**-II	None		
Singapore *Yellow Fever*-III > 1 yr A certificate is required ALSO from travelers arriving from or transiting countries in the endemic zones.			

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Slovak Republic No vaccinations are required.	None		
Slovenia No vaccinations are required.	None		
Solomon Islands *Yellow Fever*-II	All	Confirmed	B
Somalia *Yellow Fever*-II	All	Confirmed	B
South Africa *Yellow Fever*-III > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones. A certificate is required ALSO from travelers on unscheduled flights which use airports other than those used by scheduled airlines.	Rural areas (including game parks) in the north, east, and western low altitude areas of Transvaal and in the Natal coastal areas north of 28°S.	Confirmed	B

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Spain No vaccinations are required.	None		
Sri Lanka *Yellow Fever*-II > 1 yr	All areas except Colombo[14].	Confirmed	B
Sudan *Yellow Fever**-II > 1 yr A certificates is required ALSO from travelers arriving from countries in the endemic zones. A certificate may be required from travelers leaving Sudan.	All	Confirmed	B
Suriname *Yellow Fever**-II	Rural areas only, except no risk in Paramaribo District and coastal areas north of 5°N.	Confirmed	B
Swaziland *Yellow Fever*-II	All lowland areas.	Confirmed	B
Sweden No vaccinations are required.	None		

[14]Risk exists in districts of Amparai, Anuradhapura, Badulla (part), Batticaloa, Hambantota, Jaffna, Kandy, Kegalle, Kurungala, Mannar, Matale, Matara, Moneragala, Polonnaruwa, Puttalam, Ratnapura, Trincomalee, and Vavuniya.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Switzerland No vaccinations are required.	None		
Syrian Arab Republic *Yellow Fever*-II	Rural areas only, except no risk in the southern and western Districts of Deir-es-zor, and Sweida.	None	**A**
Taiwan *Yellow Fever*-II	None		
Tajikistan-Follow former USSR regulations until further notice.	Exists in southern border areas.	Suspected	A
Tanzania, United Republic of *Yellow Fever**[†]-II > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones.	All	Confirmed	B

[†]Risk in northwestern forest areas only.

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Thailand *Yellow Fever*-II > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones.	Limited risk.	Confirmed	[15]
Togo *Yellow Fever**-I > 1 yr	All	Confirmed	B
Tonga *Yellow Fever*-II > 1 yr	None		
Trinidad and Tobago *Yellow Fever**-II > 1 yr	None		
Tunisia *Yellow Fever*-II > 1 yr	None		
Turkey No vaccinations are required.	Southeast Anatolia from coastal city of Mersin to the Iraqi border (Cukorova/Amikova areas).	None	A

[15] Malaria transmission in Thailand is largely confined to forested rural areas principally along the borders with Cambodia and Myanmar (formerly Burma) not visited by most travelers; most travel to rural areas in Thailand is during daytime hours when there is minimal risk of exposure. Doxycycline is the drug of choice for travelers who overnight in the few areas with risk of malaria.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Turkmenistan-Follow former USSR regulations until further notice.	None		
Tuvalu No vaccinations are required	None		
Uganda *Yellow Fever**-II > 1 yr A certificate is required ALSO from travelers arriving from countries in the endemic zones.	All	Confirmed	B
Ukraine-Follow former USSR regulations until further notice.	None		
(Former)Union of Soviet Socialist Republics† No vaccinations are reburied.	See individual countries.		

†**Editor's note**: Presume requirements will remain the same for Russia and other newly independent states. You may check with respective embassies to be certain.

EXPLANATION OF VACCINATION CODES:

I Vaccination certificate is required of travelers arriving from ALL COUNTRIES, except as indicated in notes for individual countries.

II Vaccination certificate is required of travelers arriving from INFECTED AREAS, except as indicated in notes for individual countries. INFECTED AREAS are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

III Vaccination certificate is required of travelers arriving from a COUNTRY ANY PART OF WHICH IS INFECTED, except as indicated in notes for individual countries. INFECTED COUNTRIES are reported in the biweekly "Summary of Health Information for International Travel" (also known as the "Blue Sheet").

* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
United Arab Emirates No vaccinations are required.	Northern Emirates, except no risk in cities of Dubai, Sharjah, Ajman, Umm al Qaiwan and Emirate of Abu Dhabi.	None	A
United Kingdom (with Channel Islands and the Isle of Man) No vaccinations are required.	None		
United States of America No vaccinations are required.	None		
Uruguay No vaccinations are required.	None		
Uzbekistan-Follow former USSR regulations until further notice.			
Vanuatu(formerly New Hebrides) No vaccinations are required.	All areas except no risk on Fortuna Island.	Confirmed	B

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):

Regimen A - Routine weekly prophylaxis with chloroquine alone.

Regimen B - Routine prophylaxis with mefloquine.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Venezuela No vaccinations are required. *Yellow Fever**	Rural areas of all border states and territories and the states of Barinas, Merida, and Portuguesa.	Confirmed	B
Viet Nam *Yellow Fever*-II > 1 yr	Rural areas only, except no risk in the Red and Mekong Deltas.	Confirmed	B
Virgin Islands, British No vaccinations are required.	None		
Virgin Islands, U.S. No vaccinations are required.	None		
Wake Island(U.S.) No vaccinations are required.	None		

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* CDC recommends yellow fever vaccination for travelers > 9 months of age who go outside urban areas.

> Required only of travelers of age indicated or older.

VACCINATIONS REQUIRED AND INFORMATION ON MALARIA RISK AND PROPHYLAXIS, BY COUNTRY

Vaccination Required by the Country (Read all notes carefully)	Information on Malaria Prophylaxis		
	Areas of risk within country	Chloroquine resistance	Recommended regimen for travelers to areas of risk (See Codes)
Yemen *Yellow Fever*-II > 1 yr	All areas, except no risk in Aden and airport perimeter.	Confirmed	B
Yugoslavia(The Former Yugoslav Republic of Macedonia) (See Editor's Note below) No vaccinations are required.	None		
Zaire *Yellow Fever**-I > 1 yr	All	Confirmed	B
Zambia No vaccinations are required. *Yellow Fever**†	All	Confirmed	B
Zimbabwe *Yellow Fever*-II	All areas, except no risk in city of Harare.	Confirmed	B

Editor's note: Presume requirements will remain the same for the newly independent states. You may check with respective embassies to be certain.

†Risk in northwestern forest areas only.

MALARIA PROPHYLAXIS REGIMEN CODES (refer to Health Information for International Travel Manual for details of regimens including dosages, precautions, contraindications, and alternatives):
Regimen A - Routine weekly prophylaxis with chloroquine alone.
Regimen B - Routine prophylaxis with mefloquine.

APPENDIX 3

LABORATORY DIAGNOSIS OF MALARIA

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LABORATORY DIAGNOSIS OF MALARIA

INTRODUCTION

Definitive diagnosis depends upon demonstration of the parasites. For this purpose, the thick blood film is far superior to the thin film stained, since in light infections it may be impossible to find plasmodia in the thin film. A properly done thick film will yield three to four times as many positive findings and will reveal the plasmodia in almost all active clinical cases. However, once a diagnosis of "malaria" is made from examination of the stained thick films, it is usually necessary to examine stained thin blood films for identification of the particular malaria species present. In addition, thick films have large amounts of artifacts and therefore are more difficult to read.

Other characteristics of stained thin blood films may be suggestive of malaria. Leukocytes containing ingested malarial pigment may be seen. There is often a leukopenia with a relative increase of monocytes. In chronic cases, a sustained submaximal reticulocytosis beginning 4 to 7 days after the institution of specific therapy is suggestive.

NAVENPVNTMEDUs hold training classes on how to prepare and read slides for malaria.

PROTOCOL AND TECHNIQUES

Identification of malaria parasites requires practice even with good smears and staining techniques.

WHEN TO DRAW BLOOD FOR A SMEAR

Fingerstick smears should be drawn anytime malaria is suspected, regardless of fever spikes or time of day. If malaria is strongly suspected, and the smears are negative, keep doing smears. The worse symptoms are, the more frequently the smears need to be done. Once an hour should be the maximum frequency. As a rule, prepare thick and thin peripheral blood smears twice per day while the patient is symptomatic and at least daily during the remainder of treatment.

OBTAINING BLOOD

Freshly drawn blood is required. The specimen may be obtained by fingerstick or venous puncture. If you perform a fingerstick, follow this procedure:

1. Clean the end of the finger with a disinfectant.

2. Wipe the area vigorously with a dry cotton ball or sterile gauze pad to remove the disinfectant.

3. Lance the finger with a sterile lancet.

4. Allow the blood to flow freely from the wound; do not milk the finger.

5. Wipe away the first drop (it may contain disinfectant) and touch a CLEAN slide to the next drop that forms at the wound. The first drop will be for the thick smear and the second for the thin smear.

6. Repeat with second slide.

If you are obtaining venous blood by the vacutainer method, use a pipette and apply one drop to each slide.

CAUTIONARY NOTE:

Remember to use universal infection control precautions to prevent the transmission of hepatitis B virus, human immunodeficiency virus or other blood-borne pathogens that may be present. These should include as a minimum, using new gloves for each patient, wearing a lab coat, using a mask and eye protection if necessary, washing hands thoroughly after each patient or if contaminated with blood, and proper handling and disposal of needles, lancets and other sharp instruments that may be contaminated with blood.

MAKING SMEARS

IT IS NECESSARY TO MAKE BOTH THICK AND THIN SMEARS. The thick smear is used initially for diagnosing malaria and the thin smear for identifying the species of malaria. Thick and thin smears may be made on separate slides or on the same slide as illustrated in Figure 6, at the end of this Appendix. (Some authorities use the word "film" in place of "smear" in discussing malaria diagnosis. The terms are interchangeable. For consistency, "smear " will be used in this book.)

TECHNICAL NOTE:

The glass microscope slides used in malaria diagnosis are crucial for a correct diagnosis. The slides must be very clean to get good smears and uniform fixing and staining with virtually no background debris. All microscope slides (whether labeled "pre-cleaned" or not) must be cleaned before use with at least several ethyl alcohol washes or a soap and water wash followed by an alcohol wash to remove residual oils left after manufacture. The slides can also be cleaned by using a non-chlorinated bleach cleanser, such as "Bon Ami," a feldspar and soap cleanser. A thin water-cleanser slurry is applied with the forefinger in a circular motion to both sides of a slide, left to air dry, and the dry powder removed from both sides and edges of each slide with a lint free paper or cloth/gauze wipe.

THIN SMEARS

It is best to spread the drop of blood to make this slide first. After obtaining a drop of blood on the second slide, immediately smear it like you would any leukocyte differential smear. Intact red blood cells (RBCs) are important because they are needed to compare with the size of malaria parasites, as well as to demonstrate specific changes in size, color, and shape of the infected RBC which may be seen in infection due to certain species and which may aid in diagnosis.

THICK SMEARS

Using the corner of a clean slide, spread blood from the first slide to about the size of a dime. The drop should be just thick enough to read newsprint through it (Figure 6, end of this Appendix).

DRYING SMEARS

Allow both thick and thin smears to AIR DRY. Thin smears are generally dry adequately in 10 minutes, and thick smears in 30 minutes. If RAPID DRYING is needed it may be hastened by fanning or briefly exposing the slide to gentle heat such as that from a microscope lamp, hot air from a hair dryer, passing the slide through an alcohol lamp flame several times so that the slide is just hot enough that you can hold onto it briefly with the thumb and forefinger, or putting the slide in an incubator. Do not overheat the thick film and make identification of malaria parasites even more difficult.

FIXING SMEARS

The thin smear is fixed with methanol. Two methods can be used. The thin smear end of each slide can be dipped into reagent grade METHANOL for 5 SECONDS or the thin smear can be dabbed with a METHANOL-SOAKED cottonball for several seconds. Whichever method is used, one must adhere to the Critical Technical Note presented below.

CRITICAL TECHNICAL NOTE:

Do not accidently fix the thick smear with methanol vapors. A methanol-fixed thick smear will not hemolyze and can not be read! You can prevent this by either of the following methods:

1. Dip the thin smear slide at an angle of 30-45 degrees into methanol, covering only one half to two-thirds of the smear, for 5 seconds. Remove the slide, still at the 30-45 degree angle, and again blow gently over the slide from the thick smear end of the slide until the thin smear is dry.

OR

2. While dabbing the thin smear with the methanol soaked cottonball, blow for several seconds across the slide from the thick smear end until the thin smear is dry.

3. Send a set of thick and thin, stained and unstained slides to the nearest NAVENPVNTMEDU.

STAINING

The staining of thick and thin malaria smears is not difficult if the following procedures and precautionary notes are carefully followed:

1. Staining materials. The only reagent readily available in the supply system consists of a kit with one bottle of Giemsa stain concentrate and one bottle of buffer salts for reconstitution.

2. Preparation of working Giemsa staining solution.

a. Prepare buffered water, pH 7.2. Fully dissolve one capful (about 1 gm) of buffer salts, using the cap of the buffer salt bottle, into 1000 ml (1 liter) of distilled or deionized water to yield a final solution with pH 7.2. Check the pH with a pH meter, pH paper, or the Chlorine and pH Comparator Test Kit. Add 1.0 N sodium hydroxide (NaOH) dropwise to the 1000 ml of buffer solution, mix, and recheck the pH until pH 7.2 is achieved. A pH of 7.2 is optimal for proper staining of the

blood cells and malaria parasite elements for correct identification.

b. Giemsa stain concentrate. DO NOT SHAKE the bottled Giemsa stain concentrate prior to reconstitution with the buffered distilled or deionized water. (If the bottle is shaken, sediment in the bottom will be resuspended in the Giemsa stain concentrate).

c. Prepare working Giemsa staining solution. Combine stain and buffer in the following ratio:

1 part UNSHAKEN Giemsa stain concentrate
9 parts buffered water, pH 7.2

TECHNICAL NOTE:

Make only enough working Giemsa staining solution for the number of slides to be examined at any one time, with several extra milliliters for pipetting errors. Each slide will require 1 to 2 ml of stain. For example, if you have five slides to stain, make about 10 ml of working Giemsa by adding 1.0 ml Giemsa stain concentrate to 9.0 ml of pH 7.2 buffered water, to make a 1:10 dilution. When you use the unshaken Giemsa stain concentrate to make the working Giemsa, you DO NOT need to filter the stain.

3. Staining. Place the slides flat on a staining rack or a suitable surface. Fully cover the slide with 1 to 2 ml of working Giemsa staining solution and let it stand for 10 minutes.

TECHNICAL NOTES:

A longer staining time with a weaker working staining solution is preferable to a shorter staining time with a more concentrated working staining solution.

Rule of Thumb: 1:10 dilution stain for 10 minutes, 1:20 dilution stain for 20 minutes, 1:30 dilution stain for 30 minutes, etc.

Staining with a staining dish is not preferred because:

a. Slides standing on their edges may mechanically flake off the thick smears.

b. The film that forms on the surface of the stain will adhere to the smears upon removal from the staining dish. Rinsing with buffered water will not

sufficiently remove the film and this film will leave stain debris on the slides making it very difficult to read and interpret the slides.

c. Giemsa stain loses staining potency after repeated use.

Wright-Giemsa stain is a much less desirable alternative but may be used if Giemsa is not available. It is more difficult to see parasites with stained Wright's or W-G stain.

4. Rinsing. With the slide remaining flat on the rack, gently add enough pH 7.2 buffered water to the slide to "float" the stain off the slide. Continue adding buffered water until no more stain comes off in the rinse. Avoid vigorous rinsing, pouring or pipetting buffer directly on the smear, because the thick film/smear may slough off.

TECHNICAL NOTE:

Do not let the smears come in contact with the film that develops on the surface of the staining solution on the side. DO NOT TIP THE STAIN OFF AND THEN TRY TO WASH THE SLIDE WITH BUFFER BECAUSE THIS FILM WILL NOT WASH OFF. Two methods can help assure that the film will not be a problem:

a. Hold the slide by the corner and while keeping the slide horizontal begin to pour the buffered water rinse solution on the edge of the slide. Continue adding the rinse while tilting the slide slightly until all the color is gone.

b. While holding the slide horizontally with your fingers, let tap water run over your fingers while turning your hand and the slide over under the running water and let tap water rinse the stain off the smears which are now facing down.

5. Drying. When thoroughly rinsed, place each slide on the staining rack with the smear side down to drain and air dry. Make sure that the smear does not touch the slide rack.

READING

Malaria parasites are difficult to identify, even with good smears and staining techniques. Usually use of the oil emersion lens is mandatory. When Giemsa stain is used, the trophozoite cytoplasm stains blue in color with a ruby red chromatin dot (nucleus). Schizonts normally have three or more red chromatin

dots and some pigment which may be several colors (black, brown, yellow, green). Gametocytes have much more pigment and present only one chromatin mass. Most of the parasite will stain blue.

Each slide should be read for a minimum of 20 minutes. Often parasites are not immediately apparent, and quick visual exams are not sufficient to determine that there are no apparent parasites. Details that distinguish and identify the different malaria species are found in Table 8 at the end of this Appendix.

When malaria is suspected or identified, submit a Disease Alert Report and send a set of thick and thin, stained and unstained slides to the area NAVENPVNTMEDU for confirmation and species identification. Textbooks should be consulted to help identify parasites. (Few medical personnel see malaria parasites on a regular basis, which is necessary to maintain proficiency in parasite identification.)

CRITICAL TIPS

Short cuts, cute tricks, and sloppiness will produce more bad slides and false negative results than can ever be imagined. If you're lucky, it will be obvious you've got a problem. If you're not lucky, you'll never see the parasites that were there all along. Attention to detail <u>is</u> critical.

1. Slides must be absolutely clean, or the blood will not smear cleanly and the stain will not adhere properly.

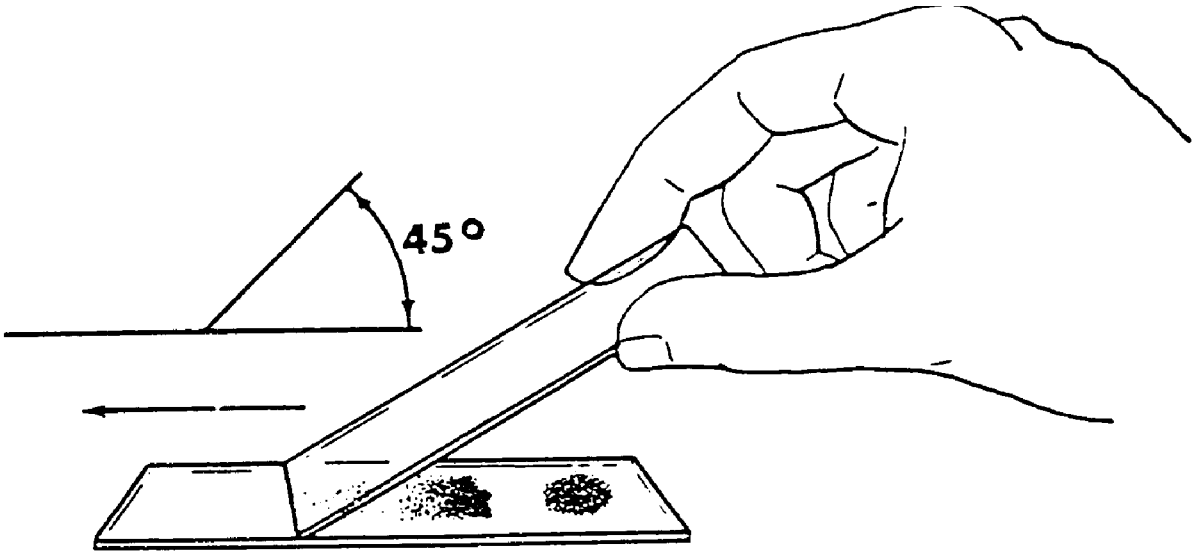
2. Heat fixing slides is like taking a drink at a party. You must know when to stop, and too many people over estimate their ability to do this. If you can't find any parasites, try again without heat fixing.

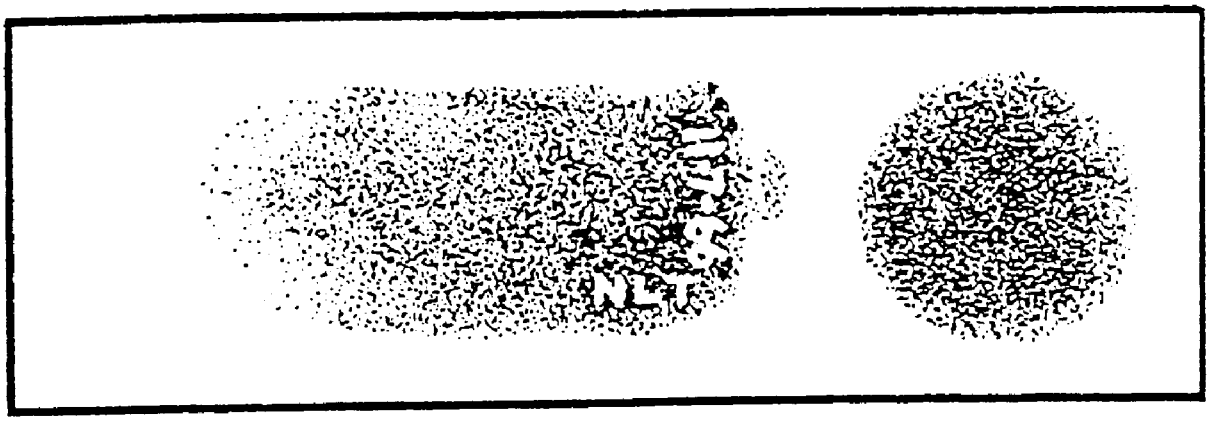
3. Stain pH is extremely important, since the stain colors change as the pH changes. If you can't find any parasites, try checking the pH.

4. Not filtering the GIEMSA stain is always a gamble, since any residue in the stain clumps on the slide and makes it much more difficult to read. With a nearly full bottle that has been sitting for a long time, the residue is nearly all at the bottom. Clean stain can be carefully poured off the top, if the bottle isn't shaken or jiggled. As the level of stain gets nearer to the bottom, it becomes harder and harder to avoid stirring up the sediment while you're pouring. Just because it looks clear doesn't mean it is. Don't forget that someone bumping into the table, or a nearby explosion, can stir up the sediment without your knowing it. If you're

having trouble reading the slide, especially if it's dirty with debris and artifacts, try again after you filter the stain.

Figure 6





in all their phases. The importance of the examination of blood films for the presence of malaria parasites will be fully understood

TABLE 8

MICROSCOPIC CHARACTERISTICS OF MALARIA SPECIES

Species	Length of Asexual * Cycle	Stages Found In Circulating Blood	Appearance of Read Blood Cell		Appearance of Parasite		
			Size	Stippling	Cytoplasm	Pigment	No. of Merozoites
Plasmodium vivax	41-47 hours, usually 43-45 (For practical purposes, cycle is considered as 48 hours)	All: Trophozoites Schizonts Gametocytes Wide range seen in a given smear	Enlarged Maximum size may be 1½-2 times normal size	Schuffner's dots may be present	Ameboid trophs Light blue Has irregular "spread out" appearance in troph stage	Golden-brown, inconspicuous	12-24 Avg = 16
Plasmodium malariae	72 hours	All: Trophozoites Schizonts Gametocytes-few Few rings usually seen. Does not stay in ring stage very long.	Normal	(Ziemann's dots rarely seen)	Rounded, compact trophs Dark blue, dense cytoplasm Band form trophs occasionally seen	Dark brown, coarse, conspicuous	6-12 Avg = 8 "Rosette" occasionally seen
Plasmodium ovale	49-50 hours	All: Trophozoites Schizonts Gametocytes	Enlarged Maximum size may be 1¼-1½ times normal size	Schuffner's dots may be present	Rounded, compact trophs Dark to medium blue Usually dense (Chromatin is large)	Dark-brown, conspicuous	6-14 Avg = 8
Plasmodium falciparum	48 hours (approximately)	Trophozoites Gametocytes (Other stages develop in internal organs)	Normal	(Maurer's dots or clefts seen infrequently)	Double dots in rings common Rings often small and delicate	Black Coarse and conspicuous in gametocytes	6-32 Avg = 20-24

* The asexual cycle is the period the parasite spends in the RBC. It begins when a merozoite enters an RBC, and ends when between 6-32 new merozoites rupture out of the RBC. The latter process produces a fever, and when synchronized among RBCs produces the "characteristic" fever spikes of malaria.

APPENDIX 4

METHODS OF COUNTING MALARIA PARASITES IN BLOOD SMEARS

APPENDIX 4

METHODS OF COUNTING MALARIA PARASITES IN BLOOD SMEARS

PERCENT METHOD

There is no standardized method. A suggested approach is to locate an area of the stained thin smear where RBCs are close to each other, but not touching. Areas should be avoided where RBCs overlap each other or are more than a few RBC diameters apart. Using the stage controls, the slide should be scanned back and forth systematically. Scan from one edge to the other. At the end of each "row", move the slide one row up, (or down), and scan back to the other edge. Continue shifting in the same direction, up or down, after scanning each row.

Three hundred to 500 RBCs should be scanned and the total number of parasitized RBCs noted. (A hand tally counter is helpful to keep track of the number of RBCs scanned.) Divide the total number of parasitized RBCs by the total number of RBCs counted, and multiply by 100, to calculate an estimated percent of RBCs parasitized.

If occasional parasites have been seen after extensive searching of the slide, but few or none are seen after scanning only 300-500 RBCs, this suggests the parasitemia rate is about 1% or less. Since only rates above 2-3% are of particular concern, there is no need to attempt to refine the estimate, by counting more RBCs, if the estimated rate is about 1% or less.

ABSOLUTE NUMBERS METHOD

NOTE. This method requires a thick smear.

The following is a practical method of adequate accuracy. It is based on the number of parasites per $\mu\ell$ of blood in a thick film, these being counted in relation to a predetermined number of leukocytes. An average of 8000 leukocytes per $\mu\ell$ is taken as the standard. Despite inaccuracies due to variations in the number of leukocytes between individuals in normal health and greater variations in ill health, this standard allows for reasonable comparisons. Before counting begins, the equivalent of 0.25 $\mu\ell$ of blood (about 100 fields, using a 7 x ocular and a 100 x oil-immersion objective) should be examined in the thick film to determine the parasite species and stages that may be present. When this has been established, a suitable counting method for positive blood films is:

1. Two tally counters are required to count parasites and leukocytes separately.

2. (a) If, after 200 leukocytes have been counted, 10 or more parasites have been identified, record the results in the record form, showing parasites per 200 leukocytes;
   (b) If, after 200 leukocytes have been counted, 9 or less parasites have been counted, continue counting until 500 leukocytes have been counted and record the parasites per 500 leukocytes.

3. In each case, the parasite count in relation to the leukocyte count can be converted to parasites per $\mu\ell$ by the simple mathematical formula:

$$\frac{\text{No. of parasites} \times 8000}{\text{No. of leukocytes}} = \text{parasites per } \mu\ell$$

   This means that if 200 leukocytes are counted, the parasites are multiplied by 40, and if 500 leukocytes are counted the parasites are multipled by 16.

4. It is normal practice to count all the species present and to include both sexual and asexual parasites together. Occasionally a separate count is made of the gametocytes of P. falciparum but when this is done, they should still be included in the general parasite count. It is rarely possible to separate the gametocytes of P. vivax or P. malariae

APPENDIX 5

THE WILSON-EDESON (W/E) TEST FOR URINARY CHLOROQUINE

APPENDIX 5

THE WILSON-EDESON (W/E) TEST FOR URINARY CHLOROQUINE

INTRODUCTION

The U.S. Army adapted the Wilson-Edeson (W/E) Test during the Vietnam conflict to identify those units which had poor malaria chemoprophylaxis compliance. A serious question sometimes exists as to whether malaria cases in the military result from lack of drug compliance or failure of the current prophylactic drugs. If drug failure occurs, adequate documentation is necessary to determine if the chloroquine phosphate drug regimen was taken. Verbal confirmation is not an adequate measurement of drug compliance.

The W/E test is approximately 90% reliable for determining the presence of chloroquine in urine. This precludes disciplinary action against any specific individual with a negative test result; however, it is the only effective method the medical department has to monitor unit prophylactic compliance and drug failure in field situations. A 10% random sample of unit personnel should be screened each week to monitor unit chemoprophylaxis compliance when chloroquine is used.

This test also should be used prior to treatment of all malaria cases when chloroquine chemoprophyloxis has been used. Documented malaria, in the presence of urinary chloroquine, may indicate a chloroquine-resistant strain. However, if the patient's W/E test is negative, it cannot be determined if the malaria is chloroquine sensitive or resistant. Pre-treatment Wilson-Edeson (W/E) Test results should be reported on a case-by-case basis on all malaria Disease Alert Reports (DAR).

MATERIALS REQUIRED FOR THE W/E TEST

TABLE 9

MATERIALS REQUIRED FOR THE W/E TEST FOR URINARY CHLOROQUINE

ITEM	NSN	QUANTITY
Potassium Iodide (USP) KI	6505-00-136-7000	1
Burner, Alcohol-self generating** 1	6640-00-410-2820	
Test Tubes, 13 mm x 100 mm	6640-00-782-6012	10-20
Test Tube, Plastic (snap cap)	6640-00-759-2152	As Needed
Clamp, Test Tube	6640-00-418-1000	2
Rack, Test Tube, Laboratory 3	6640-00-258-9210	

(wire mesh, optional)
Pipette, Dropping (Plastic) 6630-00-299-8631
1 Box

Mercuric Chloride ($HgCl_2$) OPEN PURCHASE
Hydrochloric Acid (HCl) OPEN PURCHASE

** A small can of "STERNO" or "C-RATION" heat tablets also work.

PROCEDURES FOR WILSON-EDESON (W/E) TEST

NAVENPVNTMEDUs hold training classes on how to perform Wilson-Edeson tests.

1. Collect a random urine specimen in a plastic prescription vial (6530-00-889-9028, bottle, snap on cap, 10 dram (36 ml)) two or three days after chloroquine is taken. A unit formation is the most convenient way to collect samples. Up to 150-200 samples can be handled with ease by a corpsman using the plastic vials.

2. The test is carried out in the same vial used in collecting the specimen. Excess urine is poured out until 4 or 5 ml (about 1/2 to 3/4 of an inch) of urine remains in each vial.

3. Add 2 to 4 drops of dilute (1 N) hydrochloric acid to each sample. This should clear up any turbidity present initially. Some samples may require a few more drops of acid to clear completely.

4. Add 5 to 6 drops of Mayer-Tanrets solution to each specimen.

5. Allow 20 to 30 minutes for the reaction to go to completion.

6. A whitish turbidity with a characteristic "blue haze" (much like motor oil) will appear in the samples containing chloroquine. The turbidity will be faint in some cases, but with questionable samples the results should be compared to an obviously negative sample to see any difference.

7. All negative and questionable samples should be heated in a clean test tube to just below boiling point as further confirmation. Partially immersing the original tubes in a beaker of boiling water for several minutes is also acceptable. In positive specimens, the turbidity will disappear on heating and reappear greatly intensified upon cooling. The heating procedure is very useful for faintly positive samples.

8. A specimen which develops no cloudiness or turbidity after the above steps have been carried out is read as NEGATIVE. The Wilson-Edeson (W/E) Test is about 90% sensitive. Thus, it is expected that 10% of personnel will have negative tests even if 100% of personnel are in compliance with chloroquine prophylaxis. However, if significantly more than 10% of the tested population have negative results, this indicates that problems with malaria chemoprophylaxis discipline exists.

Procedural Notes:

1. Urine must be fresh. No more than a few hours should elapse between collection and testing. No specimens should be held overnight. Direct sunlight on the samples should be avoided.

2. Heat confirmation (step 7) must have had to be used in less than 10% of the cases tested. This has cut the time needed to perform the test to a minimum.

3. As demonstrated in earlier reports, there is considerable individual variation in chloroquine excretion among individuals. Excretion also varies with the pH of the urine.

4. Protein in the urine will also be precipitated by Mayer-Tanrets reagent. It is readily identifiable, however, as the protein will not redissolve upon heating (Bence-Jones protein is an exception). Experience with several thousand samples has shown the proteinuria is not a significant enough problem to interfere with this test.

PREPARING MAYER-TANRETS SOLUTION

Make only enough solution for 3 to 4 weeks of use, since the solution may not be stable for a longer period. For example, 5 to 6 drops of solution per test equals approximately 0.3 ml, and if 200 tests are run each week for 4 weeks, than 240 ml of solution would be needed (200 x 4 x 0.3 ml = 240 ml). For this example you would follow the directions to make 250 ml of solution.

Volume of Reagent Solution	100 ml	250 ml	500 ml
Distilled or Deionized Water	100 ml	250 ml	500 ml
Potassium Iodide (KI)	4.98 gm	12.45 gm	24.9 gm
Mercuric Chloride (HgCl2)	1.36 gm	3.4 gm	6.9 gm

1. Place desired volume of distilled or deionized water in a flask.

2. Add listed amount of potassium iodide (KI) to the water and stir to dissolve.

NOTE: It is imperative that the potassium iodide (KI) be completely dissolved in water before the mercuric chloride ($HgCl_2$) is added!

3. Add listed amount of mercuric chloride ($HgCl_2$) to the completely dissolved KI above.

4. Crush all residue with a glass stirring rod. Continue stirring until dissolved. No heat is necessary. The solution will be a light yellow color.

NOTE: The final reagent solution should be stored in a brown or amber bottle as it is sensitive to light. It should be dated with a shelf-life of 3 to 4 weeks.

SOURCES OF MAYER-TANRETS REAGENTS

HYDROCHLORIC ACID

NOTE AND WARNING: Hydrochloric acid (HCl) is a corrosive liquid in concentrations above 0.1 N. It must be handled with extreme care. Do not the breathe vapors or allow the liquid to come in contact with the skin. Wear appropriate chemically resistant rubber or neoprene gloves and goggles for eye protection. When mixing acids and water follow the advice, "Do as you 'auter', add acids to water" and never the reverse!

Preparing 1.0 N hydrochloric acid solution from concentrated HCl:

1. Pour 500 ml of distilled water into a flask.
2. Slowly and carefully add 84 ml of concentrated (11.6 N) HCl to the 500 ml of water.
3. Add 416 ml of distilled water to the flask to bring the volume to 1000 ml and a final concentration of 1.0 N HCl.

NOTE: Several manufacturers offer 1.0 N HCl in one liter quantities. If you have no other need for HCl in concentrations above 1.0 N, you may want to order this prepared solution. Although 1.0 N HCl is still designated a corrosive liquid, 1.0 N HCl spills will cause less material damage and personal injury than concentrated HCl. Currently available 1.0 N solutions are listed below.

NOTE: Prices often change, those listed below are shown to provide estimates and should not be considered to be exact prices.

Hydrochloric Acid (HC1), (concentrated or 1.0 N). OPEN PURCHASE

◦ 1989 availability and price (items are not mailable; corrosive liquid, UN 1789, CAS 7647-01-0)

Concentrated HCl (36.5-38.0%; 11.6 N)

◦ J. T. BAKER, "BAKER ANALYZED" Reagent, meets A.C.S. Spec., cat. no. JT9535-2, 500 ml (1pt) single shipper pkg.; $18.18.(VWR)-1988, or cat. no. JT9530-1 500 ml (1pt) single shipper pkg.; $22.15. (VWR)-1989

◦ E. M. SCIENCE, Guaranteed Reagent; meets A.C.S.spec.; cat. no. EM-HX0603-13; 1 pt (500 ml); single shipper pkg.; $18.49. (VWR)-1988 or cat. no. EM-HX0603I-1 1 pt (500 ml); single shipper pkg.; $23.55. (VWR)-1989

◦ MALLINCKRODT, AR, A.C.S. cat. no. 2611-500*NY; 500 ml (1 pt). Individually packaged bottles; $15.75. (SP)-1989

1N HCl Solution - Any Reagent grade product is acceptable

◦ J. T. BAKER, "BAKER ANALYZED" REAGENT; 1 LITER; cat. no. JT5620-2; $21.80. (VWR)-1989

◦ E. M. SCIENCE; 500 ml; cat. no. EM-HX0604ZD-3; $11.50 (VWR)-1988. or cat. no. EM-HX0603D-3; $9.60. (VWR)-1989

◦ MALLINCKRODT, 1.0 Normal Volumetric Solution; cat. no. 6388-1*NY; 1 LITER bottle; $7.60. (SP)-1988

MERCURIC CHLORIDE

Mercuric Chloride (HgCl2) OPEN PURCHASE 1/4 lb (125 gm)

1989 available and retail price (items are not mailable; solid, poison B, UN 1624, CAS 7487-94-7)

◦ J. T. BAKER, "BAKER ANALYZED" Reagent, meets A.C.S. spec., cat. no. JT-2594-4, 125 gm, $71.55. (VWR)-1989

◦ E. M. SCIENCE, Guaranteed Reagent, meets A.C.S. spec., cat. no. EM-MX0345-4, 250 gm, $103.80. (VWR)-1989

◦ MALLINCKRODT, AR, A.C.S. cat. no. 1420-125*NY, 125 gm, (1/4 lb) bottle, $43.90. (SP)-1988

SAMPLE SUPPLIERS

- VWR= VWR Scientific, main office, P.O. Box 7900, San Francisco, CA 94120 and numerous regional offices. Tel. (415) 467-6202

SP = American Scientific Products, General Offices, 1430 Waukegan Road, McGaw Park, IL 60085-6787 and numerous regional offices. tel. (312) 689-8410

These are examples. Almost any chemical supply company can provide $HgCl_2$ or HCl. Must be reagent grade.

APPENDIX 6

IMPORTANT ANOPHELES VECTORS OF MALARIA

APPENDIX 6

IMPORTANT ANOPHELES VECTORS OF MALARIA:

1. **North America**:

   a. Southeastern - quadrimaculatus.
   b. Southwestern - freeborn.
   c. Mexico - albimanus, aztecus, pseudopunctipennis.

2. **Central America and West Indies**:

   albimanus, aquasalis, bellator, pseudopunctipennis, punctimacula.

3. **South America**:

   albimanus (Ecuador, Colombia, Venezuela), albitarsis, aquasalis, bellator, cruzii, darlingi, nuneztovari (Northern), pseudopunctipennis (Northern and Western), punctimacula.

4. **North Europe and Asia**:

   maculipennis complex (including atroparvus and messeae), pattoni (Northern China), sacharovi, Sensis (Southern China).

5. **Mediterranean-Southern Europe**:

   Morocco, Algeria, Tunisia through the Levant to the Sea of Aral: troparvus (Spain, Portugal), claviger, dthali, labranchiae, messeae, pulcherrimus, sacharovi.

6. **Desert-North Africa and Arabia**:

   hispaniola, multicolor, pharoensis, sergentii.

7. **Ethiopia**:

   a. African - arabiensis, dthali, funestus, gambiae, socki, hargreavesi, melas (West Coast), merus (East Coast), moucheti, nili, pharoensis.

   b. Yemen - culicifacies, gambiae, sergentii.

8. **Indo-Persian-Iraq, Oman, Persia, Afghanistan, Pakistan, India, Sri Lanka**:

annularis, culicifacies, dthali, fluviatilis, hyrcanus, minimus, philippinensis, pulcherrimus, stephensi, sundaicus, superpictus, varuna.

9. **Indochinese Hill Zone-Foothills of Himalayas to Hills of S. China, Burma, Thailand and Indo-China**

annularis, balabacensis, dirus, maculatus, minimus.

10. **Malaysian-Malaya, Indonesia, Borneo, Philippines, Coastal Plains from S. China to Bengal**:

aconitus, balabacensis, campestris, dirus, donaldi, flavirostris (Philippines), letifer, leucosphyrus, maculatus, minimus, nigerrimus, philippinensis, sinensis, subpictus, sundaicus.

11. **Chinese-Central China, Korea, Japan**:

lesteri, pattoni, sacharovi, sinensis.

12. **Australasian**:

bancroftii, farauti, karwari, koliensis, punctulatus, subpictus.

Bruce-Chwatt, L. J. Essential Malariology. 2nd edition, New York; John Wiley and Sons, 1985. Harwood, R. F. and James, M. T. Entomology in Human and Animal Health. 7th edition, New York; Macmillan Publishing Company, 1979.

APPENDIX 7

SAMPLE SF 600

APPENDIX 7

USS CONTINUOUS C. OPS (CVN 26)

RECORD OF MALARIA CHEMOPROPHYLAXIS

( ) Patient placed on a regimen of **DOXYCYCLINE 100 mg** (one capsule) daily beginning two days before entering malarious area, continuing during stay in malarious area, and continued for 28 days after leaving the malarious area. Patient strongly encouraged to take medication with meals.

OR

( ) Patient placed on a regimen of **MEFLOQUINE 250 mg** (one tablet) weekly beginning two weeks before entering malarious area, continuing during stay in malarious area, and continued for 4 weeks after leaving the malarious area.

Patient directed to seek immediate medical attention if experiencing malaise, myalgia, backache, headache, fever, chills, loss of appetite, dizziness, nausea, vomiting, diarrhea or fatigue.

Patient counseled that he/she will be ineligible to donate blood for three years following termination of chemoprophylaxis.

PRIMAQUINE PHOSPHATE TERMINAL PROPHYLAXIS

G6PD Deficiency Test:

( ) POSITIVE - normal amount of enzyme present

Patient instructed to take **PRIMAQUINE 15 mg** daily (one tablet) for 14 days after leaving malarious area.

( ) NEGATIVE - deficient amount of enzyme present

Patient advised to seek medical attention if experiencing signs and symptoms (described above) of malaria.

Health Care Provider Signature & Stamp

APPENDIX 8

SOURCES OF INFORMATION ON MALARIA RISK

APPENDIX 8

SOURCES OF INFORMATION ON MALARIA RISK

The risk of malaria transmission and the best recommended chemoprophylaxis regimens for given areas of the world are changing rapidly. The map in Appendix 2 will help determine if malaria is a concern in different areas of the world. For more up-to-date and detailed information on malaria risk and chemoprophylaxis for a specific port or country, contact the cognizant NAVENPVNTMEDU or NAVDISVECTECOLCONCEN, which are listed in Appendix 9.

Two readily available sources of information for current assessments of malaria transmission risk and recommended chemoprophylaxis regimens are:

Disease Risk Assessment Profile (DISRAP): These multi-page reports summarize communicable disease risks in specific countries and recommend appropriate preventive medicine measures, including malaria chemoprophylaxis. DISRAPs are prepared by the Navy preventive medicine officers at the NAVENPVNTMEDUs. They are reviewed and updated every six months. The assessments of risk are based on expected military operations and the recommendations reflect current Navy requirements and medical AMALs. Current DISRAPs can be requested by telephone call, letter, or message to the nearest NAVENPVNTMEDU or NAVDISVECTECOLCONCEN. DISRAPs are available as hard copy, or floppy disks which can be used on shipboard Medical Department computers. If floppy disks are preferred, please forward an appropriate number of blank disks.

Health Information for International Travelers: This government publication is prepared by the Centers for Disease Control (CDC), U.S Public Health Service. Its country-by-country lists of required immunizations, areas of malaria risk and recommended malaria chemoprophylaxis are especially useful for advising active duty members on leave, as well as dependents and civilians who are traveling to foreign countries. It is revised and published annually and can be purchased from Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., 20402, Telephone (202) 783-3238.

APPENDIX 9

MALARIA CONSULTANTS

APPENDIX 9

MALARIA CONSULTANTS

GENERAL POLICY AND RECOMMENDATIONS

Occupational and Preventive Medicine Division (MED-24)
Bureau of Medicine and Surgery
Navy Department
Washington, DC 20372-5120
Commercial: (202) 653-0386, 1788; DSN: 294-1788, 1789; FAX: (202)653-1895

Navy Environmental Health Center (NEHC-PM)
2510 Walmer Ave., Suite A
Norfolk, VA 23513-2617
Commercial: (804) 444-7575; DSN: 564-7575; FAX: (804) 444-3672
NAVENVIRHLTHCEN NORFOLK VA

GEOGRAPHIC AREA SPECIFIC INFORMATION - NAVENPVNTMEDUs

Information on the epidemiology of malaria, drug resistance patterns, mosquito vectors, laboratory diagnosis and confirmation

Officer In Charge
Navy Environmental and Preventive Medicine Unit No. 2
Naval Station
Norfolk, VA 23511-6288
Commercial: (804) 444-7671; DSN: 564-7671; FAX: (804) 444-1191
STU III (804) 444-0247
AOR: 100 W longitude east to 20 W longitude, including Iceland
NAVENPVNTMEDU TWO NORFOLK VA

Officer In Charge
Navy Environmental and Preventive Medicine Unit No. 5
Box 143, Naval Station
San Diego, CA 92136-5143
Commercial: (619) 556-7070; DSN: 526-7070; FAX: (619) 556-7071
AOR: 100 W longitude west to 150 W longitude including Alaska
NAVENPVNTMEDU FIVE SAN DIEGO CA

Officer In Charge
Navy Environmental and Preventive Medicine Unit No. 6
Box 112, Naval Station
Pearl Harbor, HI 96860-5040

Commercial: (808) 471-9505; DSN: 471-9505; FAX: (808) 474-9361
AOR: 150 W longitude west to 70 E longitude, except Alaska
NAVENPVNTMEDU SIX PEARL HARBOR HI

Officer In Charge
U.S. Navy Environmental and Preventive Medicine Unit No. 7
PSC 824 Box 2760
FPO AE 09623 (Sigonella, Italy)
Commercial (from within U.S.): 011-39-95-56-4099
Commercial (from within Italy): 095-56-4099
FAX: 011-39-95-56-4100
DSN: 624-4099
AOR: 70 E longitude west to 20 W longitude, except Iceland
NAVENPVNTMEDU SEVEN SIGONELLA IT

GEOGRAPHIC AREA SPECIFIC INFORMATION ON MOSQUITO VECTORS

Officer In Charge
Naval Disease Vector Ecology and Control Center
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NAVAL MEDICAL RESEARCH UNITS

These commands are part of the Naval Medical Research and Development Command and are located at various areas around the world. All conduct tropical medicine research and can provide information on the epidemiology of malaria, antimalarial drug resistance, and mosquito vectors within their geographic areas of research.

Naval Medical Research Institute
Director for Malaria Programs
12300 Washington Ave
Rockville, MD 20852

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APPENDIX 10

RECOMMENDED SUPPLIES AND TRAINING AIDS

APPENDIX 10

RECOMMENDED SUPPLIES AND TRAINING AIDS

The following is an extensive, but not all-inclusive list of items that can be used for personal protection and malaria chemoprophylaxis and treatment. Items not in the Federal Supply System may have to be purchased for special circumstances such as the development of new patterns of drug resistance of the vectors. The cognizant Navy Environmental and Preventive Medicine Unit (NAVENPVNTMEDU) or Navy Disease Vector Ecology Control Center (NAVDISVECTECOLCONCEN) must be contacted for advice on new items or items situationally required because of a unique deployment or geographical contingencies.

PERSONAL PROTECTION MEASURES

NSN	ITEM
6840-00-753-4963	Insect repellent, clothing and personal, 75 percent DEET, 2 ounces
6840-01-167-6674	Insecticide, D-phenothrin, 2 percent
6840-01-278-1336	Insect repellent, clothing, Permethrin aerosol, 6 ounce can
6840-01-284-3982	Insect repellent, personal, 35 percent DEET, 2 ounces
7210-00-266-97936	Insect Bar (netting), cot type
7210-00-267-5641	Poles, insect bar (for suspending insect bar)
8415-01-035-0846	Parka, fabric mesh, insect repellent (DEET jacket) - size small
8415-01-035-0847	Parka, fabric mesh, insect repellent (DEET jacket) - size medium
8415-01-035-0848	Parka, fabric mesh, insect repellent (DEET jacket) - size large
8415-00-935-3130	Head net, insect

ANTIMALARIAL DRUGS

6505-00-117-6450	Chloroquine phosphate tablets, 0.5 gm, 500's
6505-00-913-7905	Chloroquine/Primaquine phosphate tablets, individually sealed, 150's
6505-00-299-8273	Primaquine phosphate tablets, 1000's
6505-01-132-0257	Pyrimethamine-sulfadoxine (Fansidar(R)) tablets, 25's
6505-00-957-9532	Quinine sulfate, 325 mg capsules, 100's
6505-01-095-4175	Doxycycline, 100 mg tablets, 50's
6505-01-078-3717	Chloroquine hydrochloride, injection
6505-00-864-6298	Quinidine gluconate, injection
6505-00-074-4582	Quinine dihydrochloride, injection **
6505-01-315-1275	Mefloquine hydrochloride, tablets, 25's

** Parenteral quinine dehydrochloride is only available in limited supply through the Defense Personnel Support Center (DPSC), Philadelphia, PA. On an emergency basis, requesters must contact DPSC by the 24-hour telephone number: AUTOVON: 444-2111: Commercial:(215)-952-2111.

TRAINING AIDS

1. Bench Aids for the Diagnosis of Malaria. These consist of a set of eight glossy plates. Available from World Health Organization Publications Center USA, 49 Sheridan Avenue, Albany, NY 12210. (518) 436-9686. Cost is less than $15.00, which includes shipping and handling.

2. Audiovisual Aids

   a. 801472 DN - Vector-Borne Diseases: Our Constant Enemy.
   b. 802373 DN - Malaria Prevention
   c. 504463 DD - Disease Vector Surveillance and Control in Arid Regions
   d. 802372 DN - Insect Repellent: Do It Yourself Protection From Vector-Borne Disease.

APPENDIX 11

GLOSSARY

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GLOSSARY

anemia - A level of red blood cells lower than the lower limits of normal, as measured by such tests as a hemoglobin level or hematocrit. Malaria causes anemia by destroying red blood cells, (hemolysis), however the degree of anemia may be more than can be completely accounted for by the amount of hemolysis. See "hemoglobin" and "hematocrit."

anorexia - A lack of appetite for food. A lack of desire for, or interest in eating.

arthralgia - Pain or aching of the joints.

chemoprophylaxis - A method of attempting to prevent malaria by taking various drugs prior to, during, and after exposure to malaria. Chemoprophylaxis can be very effective, but is never 100% effective. Chemoprophylaxis is also called "suppressive treatment."

cinchonism - Side effects seen when serum levels of quinine or quinidine become excessively high. These effects may include tinnitus, headache, nausea, diarrhea, altered auditory acuity, and blurred vision. The term itself derives from cinchona bark, the original source of quinine.

clinical cure - Elimination of the malaria symptoms, without necessarily eliminating all of the malaria parasites. See "radical cure," and "suppressive cure."

comatose - A mental state of extreme unconsciousness, from which a person cannot be aroused.

cure - See "clinical cure," "radical cure," and "suppressive cure."

cyanosis, cyanotic - Bluish-purple in color.

defervescence - The reduction of a patient's abnormally elevated temperature into the normal range. This may occur suddenly and dramatically, often with significant sweating, a process in which the fever is said to have "broken." It may also occur gradually.

delirious - A mental state characterized by the expression of confused and unconnected ideas. Typically, these are expressed with great excitement and change rapidly. Illusions, hallucinations, and motor excitement may also be present.

dyspnea - Difficulty breathing.

eosinophilia - An increased number of a particular type of white blood cell called an "eosinophil." Eosinophilia is often associated with parasitic infections, but not with malaria.

erythrocyte - Red blood cell. In malaria, the word is commonly used as "erythrocytic stage" to refer to that stage in the malaria parasite's life cycle when it lives within the erythrocyte.

erythrocytic stage - See "erythrocyte.

exoerythrocytic stage - The stage in the malaria parasite's life cycle when it lives outside the red blood cells, within the liver cells (hepatocytes).

fever paroxysm - See "paroxysm."

fluid overload - A condition in which an excessive amount of IV fluids and/or blood products have been administered to a patient. In its more severe stages, it may produce pulmonary edema and various degrees of difficulty breathing. See "pulmonary edema."

fluid resuscitation - Administration of fluids, usually by IV, in an attempt to correct a loss or decrease in blood fluid volume. The loss may be actual, as with hemorrhage, profuse sweating or diarrhea, relative, or both. A relative loss of blood volume occurs when the vascular system dilates, increasing the total volume occupied by the same amount of blood. Fluid resuscitation is undertaken with a variety of IV fluids, such as normal saline, and may also include blood replacement.

flush - To appear reddish in color, due to physiologic changes.

gametocyte - The early sexual stage cells of the malaria parasite which form in the red blood cell. Both macrogametocytes ("female") and microgametocytes ("male") are formed, in separate blood cells. Gametocytes are ingested by a mosquito when she takes a blood meal. Plasmodium falciparum, alone, forms crescent or banana shaped gametocytes, obscuring the red blood cell in the process. The banana shaped gametocyte is the easiest diagnostic feature to find, when attempting to diagnose malaria, and the most reliable.

hematemesis - Vomiting of overt blood. The blood may be bright red, or old, clotted, and dark red, ("coffee grounds").

hematochezia - Passing overt blood rectally. The blood may be bright red, or dark red-black, ("devils food cake"), foul smelling, and sticky.

hematocrit - The proportion of blood made up of red blood cells instead of serum. Normal hematocrit values are 39-49% (men) and 33-43% (women), (0.39-0.49 and 0.33-0.43 in SI reference units).

hemoglobin - The chemical in the red blood cell which carries oxygen. Normal hemoglobin values are 13.6-17.2 g/dL (men) and 12.0-15.0 g/dL (women), (136-172 g/L and 120-150 g/L).

hemolysis - The destruction of red blood cells within the circulatory system. Malaria causes hemolysis when the malaria parasites rupture out of the red blood cells.

hepatocyte - Liver cell.

heptomegaly - An enlarged liver. An unusual finding in malaria.

hyperpyrexia - An extremely high fever.

hyperthermia - A significantly elevated temperature. There is no standard definition, but any temperature of 105°F (40.5°C) or greater would probably qualify.

hypnozoite - A later stage of the malaria parasite in the liver cells. After the initial mosquito bite and clearing of sporozoites by liver cells, some parasites become latent in the liver cells. They can become active months or years later, and produce a recurrent malaria attack. Apparently, only Plasmodium vivax and Plasmodium ovale are capable of developing a latent stage and forming hynozoites. Primaquine is the only commonly used drug which is active against hypnozoites.

hypoglycemia - A blood glucose level less than the lower level of normal, which is 70-110 mg/dL (3.9-6.1 mmol/L in SI reference units). Glucose levels approaching 40 and below indicate severe hypoglycemia, a life-threatening condition and a medical emergency. Hypoglycemia is not uncommon in malaria, because malaria parasitized red blood cells utilize glucose at 75 times the normal rate. In addition, treatment with quinine, and presumably quinidine, stimulates insulin secretion.

hyponatremia - A serum sodium level less than the lower limit of normal, which is 135-147 mEq/L (135-147 mmol/L in SI reference units). Serum sodium levels approaching 120 and below indicate severe hyponatremia, and are a medical emergency. Hyponatremia can be seen in malaria, and significant hyponatremia is indicative of complicated malaria, a life-threatening condition.

hypotension - See "orthostatic hypotension."

icterus - A yellow discoloration of the eyes due to an elevated bilirubin. The bilirubin must be about 2.5-3.0 mg/dL (43-51 mmol/L in SI reference units) before the first faint discoloration can been. Often identified as "scleral" icterus, because it appears on the sclera or "white" of the eye.

immune - The ability of the body to control or modify a malaria attack because of antimalarial antibodies and other protective reactions which have developed in response to previous malaria attacks. Immune individuals live in areas endemic for malaria and are repeatedly infected. The immunity they develop does not prevent or cure malaria attacks, but controls the attack so the individual has minimal or no symptoms. Such individuals typically have low levels of malaria parasites in their blood.

incubation period - The time period from when malaria parasites are first injected into a person by a mosquito bite until the person develops symptoms of malaria.

jaundice - A yellow discoloration of the skin due to an elevated bilirubin. The bilirubin generally must be above 2.5-3.0 mg/dL (43-51 mmol/L in SI reference units) before the faintest discoloration can be seen.

leukocytosis - A total white blood cell count higher than the upper limit of normal, which is 11,000 per cubic millimeter. Strictly speaking, leukocytosis refers only to an elevation in the number of polymorphonuclear leukocytes, however, because these usually make up the majority of white blood cells, if they are increased, the total white cell count is usually also increased.

leukopenia - A total white blood cell count less than the lower limit of normal, which is 5,000 per cubic millimeter. Strictly speaking, leukopenia refers only to a reduction in the number of polymorphonuclear leukocytes, however because these usually make up the majority of the white blood cells, if they are reduced, the total white cell count is usually also reduced.

lymphadenopathy - Lymph nodes which are enlarged enough to be detected by a probing touch (palpation). Lymphadenopathy is not a feature of malaria.

malaise - The patient's subjective feeling of being sick, ill, not well or not healthy. This sensation is vague, and may range from mild to severe in intensity. It may be the only symptom, or may be accompanied by other signs and symptoms. "I feel sick," "I don't feel too good," etc.

merozoite - The end product of the asexual reproductive stage (schizogony) of the malaria parasite life cycle. This takes place in the red blood cell or the liver cell. When schizogony is complete and the red blood cell ruptures, merozoites are released and travel to other red blood cells to infect them. When schizogony takes place in liver cells, merozoites released from the ruptured liver cells travel to red blood cells and infect them. With two species, Plasmodium vivax and Plasmodium ovale, merozoites released from liver cells will also travel to other liver cells and infect them.

myalgia - Pain or aching of the muscles.

obtundation - A mental state in which sensations or pain are dulled or blunted.

oliguria - Production of an abnormally small amount of urine.

oocyst - A cyst on the outer wall of the mosquito's stomach, in which sporozoites develop. When mature, the cyst ruptures, releasing sporozoites into the body cavity, where they migrate to the mosquito's salivary gland.

orthostatic hypotension - A decrease in blood pressure which occurs when an individual goes from a reclining or seated position to a standing one. A decrease of a few mm of mercury is considered normal, but decreases more than that are considered to be orthostatically induced hypotension, especially if accompanied by symptoms such as faintness, light-headedness, dizziness, and an increased pulse. Orthostatic hypotension is common in malaria.

parasitemia - The condition in which malaria parasites are present in the red blood cells. If there is no fever or other symptoms of malaria, except for an enlarged spleen, the condition is referred to as "asymptomatic parasitemia."

paroxysm - An attack, or sharp increase in intensity, of a symptom of a disease, which usually recurs at intervals. Malaria is classically described as producing fever paroxysms, sudden severe temperature elevations accompanied by profuse sweating. However the majority of cases do not show a fever paroxysm. Therefore expecting one is not useful diagnostically, and can be dangerous if waiting for one delays treatment.

petechiae - Small, flat, purplish lesions in the skin, usually 1-3 mm in diameter. They are most commonly seen when the platelet count is very low, and are due to a clotting defect. They may also be due to immune complexes deposited in the skin.

petechial rash - See "petechiae".

presumptive treatment - Administration of antimalarial drugs to a patient suspected of having malaria, but done before the results of laboratory tests for malaria are available to confirm the diagnosis.

prophylaxis - See "chemoprophylaxis."

prostration - A state characterized by an extreme loss of strength.

pulmonary edema - Accumulation of fluid in the alveolar spaces or air sacs of the lungs, due to leakage of fluid into them. This may result in difficulty breathing. It is generally due to a breakdown of the stability of the membranes lining the alveolar spaces and/or an excess amount of fluid in the vascular system, a condition known as "fluid overload."

radical treatment - Treatment intended to achieve a radical cure. Such treatment generally requires use of a drug such as primaquine which is active against the exoerythrocytic stage parasites.

radical cure - Complete elimination of malaria parasites from the body so that relapses cannot occur.

rales - Crackling sounds heard at the end of inspiration when listening to the lungs with a stethoscope. Their presence is generally considered abnormal.

RBC - Red blood cell.

recrudescence - A repeated attack of malaria (short term relapse), believed to be due to the survival of the malaria parasite within the red blood cells.

recurrence - A repeated attack of malaria after many weeks or months (or sometimes years), also called a long term relapse. It is believed to be due to a reinfection of the red blood cells from malaria parasites (hypnozoites) which have remained within the liver cells (hepatocytes), the exoerythrocytic stage.

relapse - A repeated attack of malaria, manifested by symptoms, parasitemia, or both. A repeat attack is considered a relapse only when the interval since the last attack is greater than the usual interval between fever paroxysms.

resuscitation - See "fluid resuscitation."

rigor - A severe chill, characterized by obvious shaking of the body.

sallow - Pale, reddish-yellow in color.

schizogony - The asexual reproductive stage of the malaria parasite. In the red blood cells, schizogony transforms a trophozoite into numerous merozoites. A similar process happens in infected liver cells.

scleral icterus - See "icterus."

splenomegaly - An enlarged spleen, a not uncommon finding in malaria. Often, splenomegaly can be detected by simple physical examination.

sporozoite - The stage of the malaria parasite which is injected into the bloodstream by the biting mosquito. Sporozoites are cleared from the bloodstream by the liver within about 30 minutes after the bite.

stuporous - A mental state characterized by a significant lack of consciousness, wakefulness, or awareness of one's surroundings.

suppressive treatment - Treatment intended to prevent or eliminate clinical symptoms, parasitemia, or both by the early destruction of parasites in the red blood cells. It does not necessarily prevent or eliminate the malaria parasite infection, and overt malaria may develop after the drug is stopped. Suppressive treatment is also called "chemoprophylaxis."

suppressive cure - Complete elimination of all malaria parasites from the body by means of continuous suppressive treatment.

tachycardia - A heart rate which is increased over the upper limit of normal, customarily taken as 100 beats per minute.

tachypnea - A respiratory rate which is increased over the upper limit of normal, customarily taken as 20 breaths per minute.

thrombocytopenia - A platelet count less than the lower level of normal, which is 150,000. Significantly low platelet counts are associated with clotting impairment and delay, however the platelet count generally must be below 50,000 before there is much danger of spontaneous bleeding. Thrombocytopenia is not unusual in malaria, although spontaneous bleeding is rare.

tinnitus - A ringing sound in the ears.

treatment - See "presumptive treatment," "radical treatment," and "suppressive treatment."

trophozoite - The early stage of the malaria parasite in the red blood cell.

urticaria - Hives. Numerous localized swellings in the skin. Urticaria may range from many, more or less uniform lesions, a few mm to a few cm in diameter, to large blotchy irregular swellings.

vasodilation - An increase in the diameter of the small vessels of the vascular system. The result is often an increase in the overall volume the vascular system can hold, while the actual volume of blood and serum remain the same. The net result is often a decrease in blood pressure, which may be significant.

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